

Fatigue
in neuromuscular disorders
and chronic fatigue syndrome
a neurophysiological approach

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and chronic fatigue syndrome
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een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

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List of abbreviations

AFQ	abbreviated fatigue questionnaire
AIDP	acute inflammatory demyelinating polyneuropathy
CAF	central activation failure
CFS	chronic fatigue syndrome
CIS	checklist individual strength
CVD	conduction velocity distribution
EEG	Electroencephalography
EMG	Electromyography
F_s^b	force response to stimulation before voluntary contraction
F_s^e	force response to stimulation at the end of voluntary contraction
FSHD	facioscapulohumeral dystrophy
F_s^t	estimated force response to stimulation in rest at time t
F_{sx}^t	superimposed force response at time t
F^t	actual voluntary force at time t
FSS	fatigue severity scale
GBS	Guillain-Barré syndrome
HMSN	hereditary motor and sensory neuropathy
MD	myotonic dystrophy
MFCV	muscle fiber conduction velocity
MI	primary motor cortex
MU	motor unit
MUNE	motor unit number estimation
MVC	maximal voluntary contraction
NC	nerve conduction
PF	peripheral fatigue
RP	readiness potential
sEMG	surface electromyography
SF-36	short form 36-item health survey questionnaire
SMA	supplementary motor area

Chapter 1

General introduction

Fatigue is a common phenomenon in daily life. It normally develops during exercise and is often regarded as something negative. Though, acute fatigue can be a positive experience¹⁴, for example when it develops during exercise that leads to a positive result, like winning a sports match.

A minority of people is chronically severely fatigued. In this case, fatigue may strongly influence a person's daily life, for example reducing social contacts and prohibiting work or other activities. Chronic fatigue has been described in chronic fatigue syndrome and a number of additional disorders, but clinical practice suggests that it is a common complaint also of patients with neuromuscular disorders.

Aim of this thesis

The present thesis presents a number of studies aiming to investigate fatigue in neuromuscular disorders and chronic fatigue syndrome. It is divided into four sections.

The introductory section (section 1, chapters 2 and 3) addresses the presence and impact of chronic fatigue in the patient population. The main question to be answered is if fatigue is a common symptom of neuromuscular disorders. Therefore, chapter 2 reviews fatigue literature, especially with respect to neuromuscular disorders. It introduces different types of fatigue which are important to distinguish in research: experienced fatigue, and physiological fatigue, of which the latter can be subdivided into central and peripheral fatigue. Chapter 3 investigates the frequency of chronic severe experienced fatigue in the neuromuscular disorders facioscapulohumeral dystrophy, myotonic dystrophy, and hereditary motor and sensory neuropathy. These chronic disorders were chosen because they are relatively common, genetically well-defined, and represent three different classes of neuromuscular disorders: myogenic, multisystem, and neurogenic, respectively. A model exists which explains experienced fatigue in chronic fatigue syndrome with psychological and behavioral factors¹⁸³. Especially in neuromuscular patients, however, the contribution of physiological factors to fatigue may be relevant. Namely, in contrast to chronic fatigue syndrome, a somatically unexplained disease, in neuromuscular disorders the

motor of movement is affected. The subsequent parts of this thesis concentrate on physiological aspects of fatigue. The main focus is on central aspects of fatigue, but peripheral fatigue is also discussed.

How can we measure physiological fatigue? The methodological section (section 2, chapters 4, 5, and 6) presents some methods to determine and quantify physiological aspects of fatigue. The chapters 4 and 5 show how the amount of central activation failure and central fatigue can be determined at the motor endplate with electrical stimulation during sustained maximal voluntary contractions. Chapter 6 presents a method to study central aspects of fatigue more upstream in the nervous system, namely at the motor cortex. In addition to the presentation of the methods, the section provides reference values of healthy subjects, which can be used in patient studies.

In the third section (chapters 7, 8, and 9) the methods described earlier are applied to groups of patients with chronic fatigue syndrome and a number of neuromuscular disorders to determine if experienced fatigue relates to physiological fatigue in patients. Chapter 7 studies physiological fatigue in patients with chronic fatigue syndrome, severely fatigued people without a somatically explained disease. Chapter 8 addresses fatigue in patients with the chronic neuromuscular disorders facioscapulohumeral dystrophy, myotonic dystrophy, and hereditary motor and sensory neuropathy. Finally, chapter 9 describes physiological fatigue in patients recovered from Guillain-Barré syndrome, an acute neuromuscular disorder.

In the final section of this thesis (section 4), the combined summary and general discussion (chapter 10) address the main findings and implications of this study. The main questions to be answered are:

- 1) Is fatigue a common symptom of neuromuscular disorders?
- 2) How can we measure physiological fatigue?
- 3) Does experienced fatigue relate to physiological fatigue in patients?

Section 1
Frequency of experienced fatigue
in neuromuscular disorders

Chapter 2

Fatigue in neuromuscular disorders

Adapted from:

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Abstract

Chronic fatigue is a symptom of diseases such as cancer, multiple sclerosis, Parkinson's disease and cerebrovascular disorders. Fatigue can also be present in people with no defined somatic disease. If certain criteria are met, chronic fatigue syndrome can be diagnosed. Fatigue is a multi-dimensional concept with both physiological and psychological aspects. The 'Abbreviated Fatigue Questionnaire' consisting of 4 questions is a tool to measure the level of experienced fatigue with a high degree of reliability and validity.

Within the group of patients with neuromuscular disorders, fatigue has been reported in patients with post-polio syndrome, myasthenia gravis and Guillain-Barré syndrome. The percentage of neuromuscular patients suffering from severe fatigue (64%) is similar to that of patients with multiple sclerosis, a disease in which fatigue is a well-known symptom.

Now that reliable psychological and clinical neurophysiological techniques are available, a multidisciplinary approach to fatigue in patients with well-defined neuromuscular disorders may contribute towards the elucidation of the pathophysiological mechanisms of chronic fatigue, with the ultimate goal to develop methods of treatment for fatigue in neuromuscular patients.

Introduction

Fatigue is a universal and daily phenomenon. In the general practitioner's office, symptoms of fatigue are ranked third on the list of most reported problems⁹¹. The symptom of fatigue, however, covers a difficult multidimensional concept and therefore creates a complex problem for the physician.

Fatigue as a chronic symptom is a well-known manifestation of a number of somatic disorders, like cancer, multiple sclerosis, Parkinson's disease and cerebrovascular disorders (Table 2.1). It also occurs as a side-effect of medication like β -blockers. Fatigue has been described in depression and during stress. There also is a group of severely fatigued patients that do not have a somatically demonstrable disease. If fatigue exists for more than 6 months and patients fulfill a number of additional criteria (Table 2.2), the disorder is diagnosed as chronic fatigue syndrome (CFS)⁴³. It is estimated that about 30,000 to 40,000 people suffer from CFS in the Netherlands⁶⁶. It is less well known that chronic fatigue also often occurs in neuromuscular disorders and that it has a considerable impact on these patients. Citing a neuromuscular patient: "Personally I consider fatigue as a more severe problem than the measurable somatic problems and handicaps. Fatigue makes me miss several things, whereas I could learn to live with the somatic handicaps. Despite my somatic problems I could fully function in society, if only the problem of fatigue was solved."

In the basic sciences, especially neurobiology, fatigue has been defined as a time-related force decline^{50,70}. In clinical medicine fatigue has not been investigated thoroughly until recently, possibly because the term was regarded subjective and was not

Disorder	Percentage of severely fatigued patients	Table 2.1 Percentage of patients with several disorders experiencing severe fatigue
Cancer (during treatment)	75-99 ^{87,147}	
Cerebrovascular accident (after)	51 ¹⁷⁵	
Chronic pancreatitis	73 ¹⁴	
Guillain-Barré syndrome	81-86 ¹⁰⁷	
Multiple sclerosis	57-97 ^{75,87,172}	
Myasthenia gravis	82 ¹²⁴	
Parkinson's disease	65 ⁸⁷	
Post polio syndrome	80 ⁸⁷	
Systemic lupus erythematosus	80 ⁸⁷	

To diagnose chronic fatigue syndrome the following criteria should be fulfilled

Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset (has not been lifelong) and lasts for 6 or more consecutive months
 Fatigue is not the result of ongoing exertions
 Fatigue is not substantially alleviated by rest
 Fatigue results in substantial reduction in previous levels of occupational, educational, social, or personal activities

Four or more of the following symptoms are concurrently present for > 6 months

Impaired memory or concentration
 Sore throat
 Tender cervical or axillary lymph nodes
 Muscle pain
 Multi-joint pain
 New headaches
 Unrefreshing sleep
 Post-exertion malaise

Table 2.2 Criteria for chronic fatigue syndrome⁴³

well-defined¹⁰². Now that we have a better insight into different aspects of chronic fatigue and are able to measure these reliably, subjective feelings can be studied scientifically. Therefore, researchers and clinicians more and more consider fatigue a problem worth the study^{14,87}

This chapter describes the term fatigue and how it can be measured and reviews the literature about fatigue in neuromuscular disorders.

Experienced fatigue

Asking patients or physicians to describe fatigue will lead to a variety of descriptions: e.g. sleepiness, weakness, exercise intolerance or exhaustion. Thus, the term fatigue may be confusing, especially when used in the context of neuromuscular disorders, in which weakness is usually the main symptom. This complicates the definition, diagnosis and treatment of the symptom of fatigue.

Medical literature usually defines fatigue in the sense of 'experienced fatigue': an overwhelming sense of tiredness, lack of energy and feeling of exhaustion^{14,42,77,87}. A problem arises in discriminating the level of fatigue between different individuals. Everyone knows the feeling of fatigue, but do we mean the same thing? In order to compare levels of fatigue between subjects, fatigue should be quantified. For physicians this has practical

implications, because they often need to evaluate the seriousness of the sign. This may be important to predict other symptoms or consequences of the disease, like the need for medical supplies or a reduction in working hours¹²⁵. Experienced fatigue is a concept with both psychological and physiological dimensions. For example the psychological factors well-being, concentration, attributions and social functioning may all influence experienced fatigue¹⁸² (Table 2.3).

Experienced fatigue can best be quantified with questionnaires. The Checklist Individual Strength (CIS)¹⁰ contains an eight-item subscale fatigue. It is used both for scientific research and for patient care. For clinical practice also the Abbreviated Fatigue Questionnaire (AFQ) may be used^{1,2}. This is a shortened version of the CIS, which measures fatigue with four items. It has both a good reliability and validity and has been developed to use in the general practitioner's office.

Physiological fatigue

In physiology, fatigue is usually defined as the loss of voluntary force-producing capacity during exercise¹³. Physiological fatigue is not necessarily accompanied by experienced fatigue, nor vice versa. The loss of force producing capacity can both (and simultaneously) have a peripheral and a central origin because

Type of fatigue	
Physiological	Location
Central fatigue	Brain
	Spinal cord
	Peripheral nerve
Peripheral fatigue	Neuromuscular transition
	Muscle
Psychological	
Concentration	
Restrictions in daily functioning	
Physical activity	
Attributions about fatigue (e.g. attitude, self-efficacy)	
Social support	
Social functioning	
Psychological well-being	
Sleep disturbances	

Table 2.3 Dimensions possibly influencing experienced fatigue

muscles do not function autonomically, but are activated by the nervous system (Table 2.3).

Fatigue has mostly been studied at the peripheral level, that is in the muscle tissue. Peripheral fatigue is mainly ascribed to changing intracellular ion levels having a negative effect on contractile force^{3,59,177}. During peripheral fatigue, accumulation of lactate and extracellular potassium, together with a lowering of the pH, influence membrane excitability¹⁸⁸. Therefore, muscle fiber conduction velocity reflects the peripheral situation. With the multi-channel electrode grids developed at the Department of Clinical Neurophysiology in Nijmegen muscle fibre conduction velocity can be assessed quite easily¹⁸⁷. The most direct measure of peripheral fatigue, however, is the different force response to artificial electrical stimulation during rest after exercise compared to before. This directly shows the loss of force produced by the muscle tissue after constant input into the muscle.

Central fatigue, the decrease of voluntary activation of the muscle by the nervous system, nowadays gains interest. A muscle receiving suboptimal input from the nervous system will not show its maximal force capacity. In the case of sub-maximal central activation, central activation failure (CAF) is said to be present. An increase of CAF during exercise is called central fatigue.

Sub-maximal voluntary drive may have several causes, like a lack of motivation or exhaustion of cortical neurons in the motor cortex. Usually, CAF is determined with a version of the so called twitch-interpolation technique⁴⁸ (Fig. 4.1). Subjects are instructed to make a maximal voluntary contraction (MVC) of a specific muscle. During MVC, artificial electrical stimulation is applied on the motor nerve or motor endplate. If voluntary central drive is optimal, this will not lead to additional force production. However, if voluntary activation is sub-maximal, electrical stimulation results in an increase of force. Thus, in this case CAF can be shown. With this technique, CAF can be quantified and its change over time (central fatigue) may be studied, but it cannot discriminate between the different causes of CAF.

Combining data about central and peripheral aspects of fatigue will lead to a more profound insight into the relative contributions of these aspects to physiological fatigue.

Fatigue in neuromuscular disorders

Because experienced fatigue has direct consequences for the quality of life, questionnaires like the CIS can be used in studies in which the quality of life is the main research topic¹. Although clinical research shows an increasing interest in aspects of quality of life, experienced fatigue is only sporadically included. This unfortunately is also the case for studies into neuromuscular disorders. In a number of other neurological disorders, like multiple sclerosis or Parkinson's disease, however, fatigue is well-known and accepted as a disease related symptom^{40,42,144,171} (Table 2.1).

Despite the many different neuromuscular disorders, only a limited number of symptoms occur. Muscle weakness is the most typical one. Other symptoms are pain, muscle loss, involuntary movements, myotonia, and contractures³⁰. Experienced fatigue is not the same as weakness; fatigue is an independent symptom. Patients having fatigue without weakness usually do not have a known neuromuscular disorder⁹⁴. In contrast, fatigue is not often recognized as a problem in neuromuscular disorders accompanied by weakness²⁵.

A number of patients with specific neuromuscular disorders like metabolic or mitochondrial disorders, however, do not show muscle weakness, but do show fatigue in the sense of exercise intolerance. Besides, some types of patients experience both muscle weakness and fatigue, like for example the patient cited above. A possible explanation is that the weak or atrophic muscles have to function at their (e.g. metabolic) limits⁹⁴. For these patients, daily life is so demanding that we could consider them top sportsmen in daily life. This type of fatigue has not yet been studied well.

Within the group of neuromuscular disorders, fatigue has mostly been described in patients with postpolio syndrome^{9,164}, myasthenia gravis¹²⁴, and immune mediated neuropathies like Guillain-Barré syndrome¹⁰⁷. In the last disorder, fatigue usually starts at the onset of the disease and often stays present for months in spite of total recovery of the peripheral nervous system. In myasthenia gravis peripheral fatigue has been studied and explained only part of the experienced fatigue¹²⁴.

As a first investigation preceding the extensive study presented in the next chapter, our group has compared experienced fatigue, functional limitations, psychological well-being and depression in 64 consecutive patients with a neuromuscular disorder visiting the outpatient clinic of our hospital and in 94 patients with multiple sclerosis⁷⁵. 64% Of the patients with a neuromuscular disorder and 57% of those with multiple sclerosis experienced severe fatigue. Thus, experienced fatigue appears equally in patients with neuromuscular disorders and multiple sclerosis. Though, in multiple sclerosis fatigue is generally accepted, whereas it is not in neuromuscular disorders. To optimize care for patients with neuromuscular disorders it is important to recognize these high percentages of fatigue and to understand the underlying pathophysiological mechanisms.

Chapter 3

Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy and HMSN-I

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Abstract

This study was developed to assess the prevalence of severe fatigue and its relation to functional impairments in daily life in patients with relatively common types of neuromuscular disorders. 598 patients with a neuromuscular disease participated (139 with facioscapulohumeral dystrophy, 322 with adult-onset myotonic dystrophy and 137 with hereditary motor and sensory neuropathy type I). Fatigue severity was assessed with the Checklist Individual Strength (CIS-fatigue). Functional impairments in daily life were measured with the short form 36-item health survey questionnaire (SF-36).

The three groups of patients with a neuromuscular disorder were of similar age and sex. Severe experienced fatigue was reported by 61-74% of the patients. Severely fatigued patients had more problems with physical functioning, social functioning, mental health, bodily pain, and general health perception. The effects of fatigue differed between the three disorders.

In conclusion, severe fatigue is reported by the majority of patients with relatively common types of neuromuscular disorders. Because experienced fatigue severity is associated with the severity of various functional impairments in daily life, it is a clinically and socially relevant problem in this group of patients.

Introduction

Fatigue has been defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion and is not the same as weakness⁸⁷. Fatigue is a common symptom in several neurological disorders such as multiple sclerosis, Parkinson's disease and stroke^{40,42,77,87,102,144,175}. In these patient populations it was found that the experience of severe fatigue can be a major determinant of disability and influences the quality of life. Surprisingly, fatigue in neuromuscular disorders has received little attention, although there have been studies in patients with particular neuromuscular disorders. Paul et al. showed that 82% of a group of patients with myasthenia gravis reported fatigue as a regular symptom of their disease¹²⁴. A study of Berlly et al. showed that 68% of a group of post-poliomyelitis patients reported daily fatigue. Half of these fatigued patients noted that their fatigue had led to the need for assistance in daily life⁹. In a group of patients with immune-mediated polyneuropathies it was found that fatigue was a prominent and highly disabling symptom¹⁰⁷. Herlofson and Larsen showed that fatigued patients with Parkinson's disease reported more problems in areas of functional limitations⁶⁹. Fisk et al. found that fatigue had a significant effect on the general health status in patients with multiple sclerosis³⁹. The impact of fatigue in health related quality of life in patients with neuromuscular disorders has not been studied so far.

Clinical experience and preliminary findings of our research group indicated that many patients with a neuromuscular disorder experience severe fatigue and consider it an important problem¹⁷¹. Most psychological studies in neuromuscular disorders, however, have focused mainly on disability or loss of quality of life, and did not address the problem of experienced fatigue among different neuromuscular disorders^{126,128,167}. Currently, no cross-sectional study has compared the presence and severity of fatigue in various neuromuscular disorders using validated instruments.

This study concerns three genetically well defined, homogeneous, and large populations of patients with relatively common neuromuscular disorders, namely facioscapulohumeral muscular dystrophy (FSHD), adult-onset myotonic dystrophy (MD)

and hereditary motor and sensory neuropathy type I (HMSN-I). FSHD is an autosomal dominant inherited myopathy¹²². MD is the most common form of muscular dystrophy and is an autosomal dominant hereditary multisystem disease involving skeletal muscles, eye, heart, lungs, gastrointestinal tract, bone, skin, and central and peripheral nervous systems⁶⁴. HMSN-I is the most common genetic disorder affecting the peripheral nervous system^{46,61,62}. Thus, this study compared experienced fatigue in patients with three different neuromuscular disorders, including a myopathy, a multisystem disorder and a neuropathy.

Our research group has developed a multidimensional assessment method to measure fatigue in several chronic disorders^{31,148,175,181,182}. In this study, in addition to fatigue severity we investigated the relation between fatigue and functional impairment in daily life.

Health-related quality of life scales, such as the short form 36-item health questionnaire (SF-36), might be useful to assess important domains of health and various aspects of impairment from the patient's perspective¹⁷⁶. We chose the SF-36, the most widely used generic health related scale, to evaluate the potential impact of fatigue on different components of functional impairment in daily life in patients with a neuromuscular disorder.

In this article we address the following questions. How many patients with these neuromuscular disorders experience severe fatigue? Are there differences in fatigue severity, demographical variables, and various functional impairments between the different neuromuscular disorders? And what is the contribution of physical functioning, social functioning, mental health and bodily pain to fatigue severity in three relatively common neuromuscular disorders?

Methods

Patients

Adult patients aged 18 to 65 years with a definite diagnosis who could be classified into one of the three neuromuscular disease categories (FSHD, MD, HMSN-I) were asked to participate. Some of the patients were recruited from the Neuromuscular Centre,

Radboud University Nijmegen Medical Centre in the Netherlands. The remainder was recruited from the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland, VSN).

In total, 900 patients were informed by a letter and received a booklet with questionnaires (described below) at home. Subjects were asked which diagnosis had been made and if this was done by a neurologist or clinical geneticist.

We used a cross-sectional design to assess fatigue in patients with a neuromuscular disorder. Written information about the purpose of the study was provided to all the patients. The study was approved by the local ethics committee.

Fatigue severity

The Checklist Individual Strength (CIS) is a 20-item questionnaire and measures the following four separate aspects of fatigue during the previous two weeks: fatigue severity (eight items, score range 8 to 56), concentration problems (five items, score range 5 to 35), reduced motivation (four items, score range 4 to 28), and reduced activity (three items, score range 3 to 21). Each item was scored on a seven point Likert scale. High scores indicated high levels of fatigue, high levels of concentration problems, low motivation, and low levels of activity (22). The CIS had good internal consistency and split-half reliability³⁵. A CIS-fatigue score of 35 or more was used to identify severe fatigue¹⁸⁰.

Functional impairment in daily life

The following subscales of the SF-36 were used to assess different areas of functional impairments in daily life: physical functioning, social functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, mental health, bodily pain, and general health perception¹⁸⁴. The transformed scores for all SF-36 scales ranged from 0 to 100. For each subscale a higher score indicated better functioning or less pain.

Statistics

Data analysis was carried out using SPSS for Windows (version 11.0). Descriptive statistics were used to describe the sample.

Normality was tested according to the Kolmogorov-Smirnov test. We used t-tests, chi-square and one-way analysis of variance (ANOVA) to test for differences between groups. In case overall significance was shown, the Bonferonni correction was applied to compare the three patient groups. Probability (p) values of ≤ 0.05 were regarded as statistically significant. Correlations were calculated with the Pearson coefficient (r). In order to examine the contribution of physical functioning, social functioning, mental health, and bodily pain in relation to fatigue severity, linear regression analyses (enter method) were performed.

	FSHD N=139	MD N=322	HMSN N=137
Age (years) (mean (SD))	43.7 (10.1)	43 (10)	42.5 (10.7)
Age range (years)	22–61	18–63	19–63
Sex (M/F) (%)	49% / 51%	47% / 53%	41% / 59%
Marital status			
Married/living together	74%	70%	69%
Single	25%	30%	31%
Missing information	1%	---	---
Education level (%)*			
Low	32%	53%	28%
Intermediate	34%	28%	27%
High	34%	19%	29%
Missing information	1%	---	---

*significant difference between MD and FSHD and between MD and HMSN (p-value < 0.05)

Table 3.1. Demographic characteristics of patient groups

Results

From the 647 adult patients (72%) who returned the questionnaires, 49 patients were excluded for the following reasons: no diagnosis of FSHD, MD or HMSN-I (n=30), incomplete booklets (n=19). A total of 598 patients fitted the inclusion criteria and completed the questionnaires (66%). This group consisted of 139 patients with FSHD, 322 with MD, and 137 with HMSN-I. Diagnoses in a quarter of these patients were made at our hospital according to established criteria³⁷. Results from this subgroup did not differ from the results of the group as a whole. Demographic characteristics of the three groups are listed in Table 3.1. No significant differences were found in age, sex, or marital status

between the three groups. The MD group had a significantly lower level of education than the two other groups.

Fatigue and functional impairment in FSHD, MD and HMSN

All patient groups experienced high levels of fatigue. The mean (SD) CIS-fatigue score in the FSHD group was 36.5 (12.5), in the MD group 40.4 (11.8), and in the HMSN group 37.4 (12.2). In the FSHD group 61% was severely fatigued, in the MD group 74%, and in the HMSN group 64%.

Table 3.2 shows a comparison of functional impairments in daily life between the three patient groups. The MD group reported having significantly more concentration problems, higher levels of reduced motivation, and reduced levels of activity. The MD group perceived lower general health but experienced less bodily pain than the FSHD and HMSN patients.

Age related problems

In the FSHD group and MD group, age correlated significantly with fatigue severity (FSHD: $r=0.19$, $p=0.002$; MD: $r=0.17$, $p=0.002$). In all three patient groups, higher age was associated with more impairment in physical functioning and more bodily pain. Among

	FSHD N=139	MD N=322	HMSN N=137	p-value
CIS				
CIS-fatigue	36.5 (12.5) ^b	40.4 (11.8) ^{a,c}	37.4 (12.2) ^b	0.002
CIS-concentration	12.3 (8.2) ^b	16.8 (8.3) ^{a,c}	13.8 (8.7) ^b	0.000
CIS-motivation	12 (5.9) ^b	16.8 (6.6) ^{a,c}	12.2 (6.1) ^b	0.000
CIS-activity	10.1 (5.5) ^b	13.2 (5.6) ^{a,c}	9.4 (5.5) ^b	0.000
SF-36				
physical functioning	45.2 (31.4)	48.4 (28.2)	53.1 (26.4)	ns
social functioning	71.6 (24.2)	69.9 (24.3)	67.5 (24.3)	ns
role limitations physical	47.9 (42)	48.2 (39.7)	48.9 (39)	ns
role limitations emotional	69.5 (41.6)	73.9 (37.6)	67.4 (41.6)	ns
mental health	72.6 (17)	72.7 (18)	68.9 (19.2)	ns
bodily pain	66.6 (23.8) ^b	75.4 (25.3) ^{a,c}	68.5 (25.5) ^b	0.001
general health perception	51.7 (21.6) ^b	40.5 (22.3) ^{a,c}	52.5 (20.7) ^b	0.000

Values are mean (SD). A higher value indicates more complaints or impairments

^aSignificantly different from FSHD, Bonferonni $p<0.05$

^bSignificantly different from MD, Bonferonni $p<0.05$

^cSignificantly different from HMSN, Bonferonni $p<0.05$

Table 3.2 The main outcome measures in the three patient groups

the MD patients, age correlated significantly with all subscales of the SF-36 and with reduced motivation and reduced activity on the CIS.

Severely fatigued patients

Severely fatigued patients (CIS-fatigue ≥ 35) were compared with less fatigued patients (CIS-fatigue < 35) within the three neuromuscular disorders. Severely fatigued FSHD patients, MD patients, and HMSN patients had more concentration problems, higher scores on reduced motivation and reduced levels of physical activity. Severely fatigued patients also had significantly lower scores at all subscales of the SF-36.

Contribution of different dimensions to fatigue severity

Regression analyses were carried out to examine the contribution of different dimensions in relation to fatigue severity (Table 3.3). Separate analyses were done for each group, with CIS-fatigue as the dependent variable. In the FSHD group, physical functioning, social functioning and bodily pain contributed significantly to fatigue severity; in the MD group, physical functioning and social functioning contributed significantly; in the HMSN group, none of the independent variables contributed significantly. The correlations between CIS-fatigue and the SF-36 subscales were weaker in the HMSN group than in the FSHD or MD group.

Discussion

As far as we know this is the first cross sectional study in which experienced fatigue has been investigated in three large homogeneous groups of neuromuscular disorders with validated

Dependent variable CIS-fatigue severity	FSHD Beta	FSHD p	MD Beta	MD p	HSMN Beta	HMSN p
Independent variables						
physical functioning	-0.228	0.010	-0.398	0.000	-0.188	0.056
social functioning	-0.219	0.038	-0.157	0.015	-0.107	0.358
mental health	-0.031	0.725	-0.112	0.048	-0.166	0.121
bodily pain	-0.195	0.042	-0.062	0.284	-0.146	0.121
age	0.022	0.900	-0.087	0.114	-0.148	0.083
Total R ² (adjusted)	0.238		0.270		0.143	

Table 3.3. Linear regression analysis to predict fatigue severity

measurements. Our study shows that 61-74% of the subjects in the investigated groups were severely fatigued. This means that the experience of severe fatigue is a major complaint in most patients with these neuromuscular disorders. In all three groups, being severely fatigued was associated with greater levels of functional impairment in daily life.

The results also showed that patients with MD had significantly higher scores of severe fatigue, reported more problems with concentration (CIS-concentration), and had more difficulty in initiating and planning (CIS-reduced motivation) than the two other groups. Daytime sleepiness is an established clinical manifestation of MD^{64,65,132}. It is possible that patients with this disease confuse the experience of fatigue with daytime sleepiness, which may have affected the CIS-fatigue scores of the MD group. However, Van der Werf et al. showed that experienced fatigue, measured with the CIS-fatigue, and daytime sleepiness are different clinical manifestations in MD¹⁷³.

In addition, we found that MD patients had a lower education level than the FSHD and HMSN patients. These differences may be explained by disease specific problems associated with a multisystem disorder such as MD. Mental dysfunction – such as reduced intelligence and lower levels of concentration and initiation- has been recognised in MD^{64,65}, in contrast to the lack of such defects in other disabling neuromuscular disorders.

Patients with FSHD and HMSN turned out to have higher scores of bodily pain than the MD patients. These results are consistent with reports of the presence of pain in other studies in FSHD and HMSN^{126,128,167}. Pain, particularly back pain, is often considered as a problem but has been poorly studied in MD patients⁶⁵.

Age and fatigue severity did not seem to be related in any of the groups, as no contribution of these variables was found in the regression analyses. Karlsen showed that fatigue severity is not regarded as part of the normal aging process⁷⁷.

The significant correlations between age and functional impairment in daily life suggest that older age is associated with increasing impairment in physical functioning and bodily pain in all three patient groups. This is in accordance with the progressive nature of these disorders. An increase in physical limitation with

age in these conditions is well-known^{46,64,122}. In MD, age is also correlated with all other functional impairments. These results are in line with the known differences between these three neuromuscular disorders^{64,65}.

Compared with the healthy control data provided in the manual of the Dutch version of the SF-36¹⁷⁶, the mean scores for our three groups of patients were reduced on all SF-36 subscales. In addition, the severely fatigued patients in all three groups scored lower than the non-severely fatigued patients, suggesting a relation between fatigue and functional impairment. Herlofson and Larsen showed that fatigued patients with Parkinson's disease reported more problems in areas of functional limitation and that patients with fatigue had more advanced disease than those without fatigue, measured by a disease severity scale for Parkinson's disease⁶⁹. A study of Fisk et al. found that fatigue had a significant effect on general health status in patients with multiple sclerosis³⁹. They showed that disease classification and neurological impairment had little bearing on fatigue in patients with multiple sclerosis. In our study we did not use a disease severity scale, so we could not investigate the relation between fatigue severity and disease severity in these disorders.

Regression analyses suggested that physical functioning, bodily pain, and social functioning were related to fatigue severity in FSHD patients. In MD patients only physical functioning and social functioning were related to fatigue severity. In HMSN patients none of the dimensions contributed independently to fatigue severity. Thus in the latter group fatigue is less clearly related to functional impairment. Possibly, factors that we did not measure play a more prominent role in the contribution of fatigue in HMSN.

The impact of fatigue in health related quality of life in patients with neuromuscular disorders has not been studied so far.

There are some methodological limitations to our study. First, its cross-sectional design makes it impossible to draw conclusions on the direction of the association. Second, not all the diagnoses were made at our hospital. About a quarter of the patients in the study came from our hospital and the diagnoses of those patients were checked. Nevertheless, this group of patients did not differ in any

of the main outcome variables from the remaining patients recruited from the Dutch Neuromuscular Diseases Association.

Conclusions

Our study shows that the majority of a large sample of patients with relatively common types of neuromuscular disorders experience severe fatigue. The factors related to fatigue severity appear to differ in the three types of disorder. Severe fatigue is associated with serious impairment in daily life. Therefore this symptom is a clinically and socially relevant problem in patients with a neuromuscular disorder.

Section 2

Methods to measure physiological fatigue

Chapter 4

Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort

Adapted from:

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Abstract

Local muscle fatigue can originate from both peripheral and central factors. The relative contribution of these factors in the course of a fatiguing contraction in 20 healthy subjects was determined.

While subjects made a 2-min sustained maximal voluntary contraction (MVC) of the biceps brachii, muscle fibre conduction velocity (MFCV) was determined with surface electromyography (sEMG) as a representation of developing peripheral fatigue. To quantify the amount of peripheral fatigue, the force development following a train of electrical stimuli on the endplate before and after the contraction were compared. To measure force loss caused by central factors, superimposed electrical stimulation was used during the contraction. By two different methods the influence of peripheral fatigue on the superimposed force responses was taken into account. The first method compared the force response with the actual voluntary force, the second -which seemed more valid- used an estimation of peripheral fatigue based on linear interpolation between the force responses during rest before and after sustained contraction. During the contraction, voluntary force decreased to 38%. Peripheral fatigue was responsible for the larger part of this decline (89%). The other part, which was calculated as 12%, was caused by an increase of central activation failure. The decline of MFCV indicated that peripheral fatigue increased predominantly during the first half of the contraction and stayed at a constant level during the latter part. In contrast, central fatigue mainly induced a force decrease in the second part of the contraction. The different mechanisms which could be responsible for this change of emphasis from peripheral to central factors are discussed.

Introduction

Local muscle fatigue is mostly defined as a reduction of the maximal force generating capacity of a muscle induced by exercise⁴⁸. Peripheral sites of the origin of fatigue include the neuromuscular junction, the sarcolemma and the contractile apparatus, while mechanisms involved may be the excitation-contraction coupling, accumulation of metabolites and depletion of fuels⁸³.

Quantification of peripheral fatigue after a sustained fatiguing contraction has been done by studying the response of a relaxed muscle upon electrical stimulation^{49,78,168}. With the same technique, the development of peripheral fatigue has been examined during periods of relaxation in repetitive contractions¹⁰⁰.

The appearance of peripheral fatigue during a contraction, has mostly been studied with electromyography (EMG). Median or mean power spectrum frequencies were shown to decrease during sustained maximal voluntary contraction (MVC)^{86,113}. Zwarts and Arendt-Nielsen showed that muscle fibre conduction velocity (MFCV) decreased during maximal effort¹⁸⁶, which contributes to this decline of power frequency¹⁶². The decline of MFCV reflects the accumulation of metabolic byproducts^{16,29,97,105} and thus can be used as a measure of peripheral fatigue. Thomas et al. showed that changes in M-wave parameters were not sufficient to detect peripheral fatigue¹⁶⁸. The reason might be that M-wave duration is an indirect rather than direct measure of conduction velocity. Magnetic resonance spectroscopy has the ability to measure the metabolic situation of the muscle during exercise more directly^{71,78}.

Besides peripheral factors, a failure of drive from the central nervous system also may contribute to the loss of force induced by exercise^{49,51,78,80}. This central fatigue can have its origin in all structures above the neuromuscular junction (central nervous system and peripheral nerves). It might result from a combination of intrinsic motoneuronal properties, reflex inhibition and disfacilitation, Renshaw cell inhibition, and insufficient drive from supraspinal sites⁴⁷, for example because of a lack of subject motivation⁴.

A few methods have been developed to detect the failure of central drive. Gandevia et al. showed that central fatigue occurred during prolonged MVC using transcranial magnetic stimulation⁴⁹. However, the non-specificity of this technique complicates quantification. Several authors have therefore used electrical stimulation of motor nerves or motor endplate regions during voluntary contractions^{4,12,49,51,78,80,100,110}. If electrical stimulation resulted in a force response, voluntary activation apparently was less than maximal.

The majority of these studies determined the amount of central fatigue during short MVC or only at the beginning and at the end of sustained MVC^{4,51,78,80,100}. As far as we know, the change of central activation in the course of a sustained contraction has only been studied by Bigland-Ritchie et al.¹², Thomas et al.¹⁶⁸ and Gandevia et al.⁴⁹. The first study did not find any central activation failure (CAF) in adductor pollicis. The second showed that at the beginning of a 5-min sustained MVC of tibialis anterior and first dorsal interosseus muscles central activation was kept optimal, but substantial failure occurred during the latter 3 minutes. Gandevia's group was the only one that showed the development of central activation failure (CAF) during a sustained maximal contraction in biceps brachii⁴⁹. They presented the superimposed force responses as a percentage of the voluntary force. This method did provide good insight into the development of central fatigue, but did not allow quantification of force loss caused by CAF.

Only a few studies exist investigating the course of both central and peripheral fatigue simultaneously during an isometric sustained MVC. Thomas et al.¹⁶⁸ did measure both fatigue modalities, but admit that the use of superimposed M-waves does not sufficiently expose the peripheral contribution. Their second technique, electrical stimulation during short interruptions while cuffs preserved the muscle in an ischemic condition, did provide a better measure of peripheral fatigue. These interruptions were made with 1-min intervals. Quantification of peripheral fatigue with a higher time resolution could be valuable.

Quantification of the contributions of both fatigue modalities during maximal effort can be of significance in a clinical setting: many neuromuscular patients complain about fatigue. Knowledge

concerning the factors responsible for fatigue in healthy controls could contribute to the development of tools for a better understanding of the phenomena that underlie the various fatigue complaints that are as yet difficult to grasp.

Accordingly, the goal of this study was to find the relative contributions of central and peripheral factors to fatigue during a maximal sustained 2-min voluntary contraction in healthy subjects using electrical stimulation and MFCV measurements simultaneously. The contribution of central factors was calculated by two different methods, whose advantages and disadvantages are discussed.

Methods

Subjects

Twenty (13 male, 7 female) healthy subjects, ranging in age from 19 to 53 years (mean 29.4 (9.2) (SD) years), participated in this experiment. None of these volunteers had a history of neuromuscular problems. In 18 of them surface electromyography (SEMG) measurements were made (11 men, 7 women). The protocol was approved by the local ethics committee. All subjects gave their informed consent.

Experimental set-up

Force recording

Subjects sat in a chair, their left arm fixed in an arm flexor dynamometer in the horizontal position with the shoulder in abduction, the elbow in a right angle and the forearm supinated. The trunk was stabilized at the thoracic level. Using strain gauges, the force of elbow flexion was measured at the wrist. Force was sampled at a rate of 2 kHz using an A/D board (Keithly Metrabyte: DAS 1602), low-pass filtered (1 kHz) and stored on hard disk of a standard PC for off-line analysis. The maximal resolution of force measurement was 0.1 N bit^{-1} .

SEMG recording

SEMG measurement was performed with a multi electrode array consisting of five electrodes that were gold coated and placed in

line (electrode diameter 2 mm; inter electrode distance 3 mm). The electrode array was placed parallel to the fibre direction of the biceps brachii muscle, distal to the motor points after the skin had been rubbed with electrode cream. A reference electrode was placed at the elbow joint. To investigate the accuracy of the SEMG electrodes placement, cross correlations between the bipolar signals were determined on-line during slight contraction.

Five monopolar signals were amplified, band-pass filtered (3.2-800 Hz) and A/D-converted (16 bits with a resolution of 0.5 mV bit^{-1} at a rate of 4 kHz/channel) using a 64-channel amplifier system (MARK 6, Biosemi, Amsterdam, The Netherlands). Data were stored on the hard disk of a standard PC for off-line analysis (see below).

A custom-made time code generator was connected between the PC used for force recordings and the one used for SEMG recordings in order to synchronize force and SEMG data.

Electrical stimulation

Electrical endplate stimulation was applied with a general purpose electrical bio-stimulator, designed and manufactured by the local Department of Technical Engineering, via a self-adhesive 93x8 mm (usually shortened to avoid co-stimulation of other muscles) cathode over both motor points of the medial and lateral head of the biceps brachii and an anode (\varnothing 32 mm) (Teca NCS electrode system 2000) at the proximal muscle belly.

As the basic 'unit of stimulation' a 40-ms stimulus train (ST) of five rectangular pulses (each pulse had a duration of 100 ms), with 10-ms intervals (100Hz) was used (Fig. 4.1). Five STs were combined to form a stimulus event (SE; inter-train interval 300 ms). So, a SE lasted 1240 ms, leading to five subsequent force responses, which were averaged. This average is referred to as the force response. Stimulated force during rest (see below) was derived from a SE with an inter-train interval of 1 s. From pilot experiments it was concluded that these stimulus characteristics were appropriate for detecting central fatigue without being too uncomfortable with reference to future use in large numbers of patients.

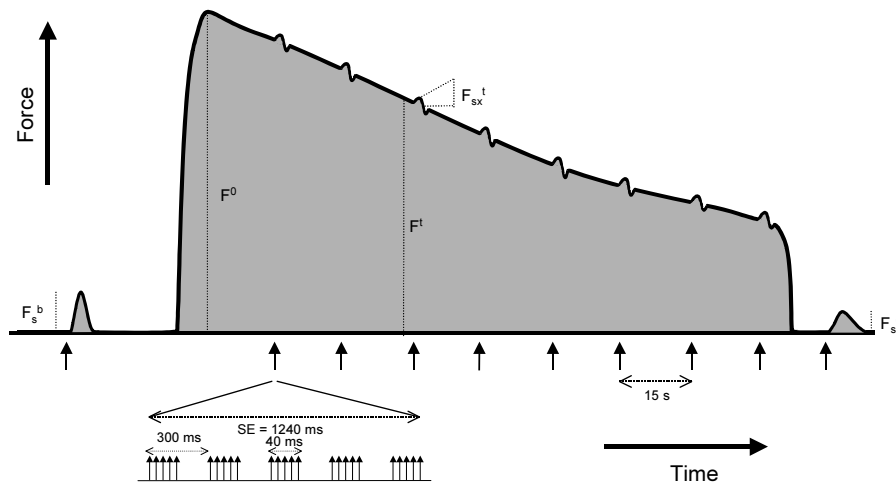


Fig. 4.1 Definition of force parameters. Vertical arrows represent electrical stimulation. (F_s^b initial force response, F_s^t superimposed force response during MVC after t s sustained contraction, F_s^e final force response, F^0 voluntary force at the beginning of sustained contraction, F^t voluntary force after t s sustained contraction, SE stimulation event)

Before the experiment, for every subject stimulus optimization was performed by slowly increasing the intensity, until no further increase of force response resulted from the increase of intensity. All SEs were given at this intensity level (23-92 mA).

Special attention was given to prevent possible co-stimulation of adjacent muscles. If co-stimulation was present, identified by palpating the muscle (triceps or deltoid), the anode was repositioned.

Protocol

While the subject's biceps brachii muscle was relaxed an initial SE was applied (Fig. 4.1), which caused the initial force response. Then, the subject performed a sustained 2-min MVC of the biceps brachii muscle. SEs were given every 15 s, leading to superimposed force responses. Loud verbal encouragement was given throughout the 2-min maximal effort and force was visually fed back to the subject. Immediately after the sustained contraction, a final SE was applied, resulting in the final force response.

Data analysis**Force**

To be able to use superimposed force amplitude as a measure of central fatigue, the amplitude has to be corrected for the peripherally induced force decline. Therefore, the size of the superimposed force during a 2-min sustained contraction was expressed in two different ways:

Method 1. Relative to the actual voluntary force. This actual voluntary force was the force averaged from 2-s recordings, measured just before the SE. In this method:

$$\text{CAF_1}^t = (F_{sx}^t / F_s^b) / (F^t / F^0) * 100\%$$

where CAF_1^t is the central activation failure at t s of sustained contraction; F_{sx}^t is the amplitude of the superimposed force response during voluntary contraction, which was corrected for changes of voluntary force via linear interpolation between the moment of stimulation and 300 ms after; F_s^b is the amplitude of the initial force response (while the arm was relaxed); F^t is the actual voluntary force and F^0 is the voluntary force at the beginning of sustained contraction (see Fig. 4.1).

Method 2. As a percentage of an estimated, 'expected' stimulated force, obtained by linear interpolation between the amplitudes of the initial and final force responses, thus:

$$\text{CAF_2}^t = F_{sx}^t / (F_s^b - t/120 * (F_s^b - F_s^e)) * 100\%$$

where F_s^e is the amplitude of the final force response (while the arm was relaxed; see Fig. 4.1).

To analyse changes in CAF over time, for each subject linear regression was performed. Then, a student's t-test was used to test if the average slope of all subjects' regression lines was larger than zero.

From the initial and final force responses, duration was defined as the period for which the force was higher than half maximum. Also maximal contraction and relaxation rates were determined, expressed as the amount of force maximally gained or lost per millisecond (relatively to the force response amplitude). A paired t-test was used to compare initial and final force response parameters.

One subject was excluded from force analysis, because his elbow was not properly fixed in the dynamometer and superimposed force responses deviated more than three standard deviations from the mean responses of all subjects.

SEMG

SEMG values used were calculated from 2 s at the very beginning of exercise and from 2 s of data just before stimulation. Cross correlations from two bipolar signals (inter-signal distance 6 mm) were determined according to Naeije and Zorn¹¹⁵. The combination of electrodes showing the highest cross correlation was chosen for further analysis, but only if cross correlation exceeded 0.7. MFCV was calculated from the phase difference spectrum of the two bipolar signals⁹⁸. This method determines a linear least-squares fit to the relation between frequency and the phase difference between the two bipolar signals. From this fit the time delay between these signals can be calculated. Relating this delay to the inter-signal distance leads to a MFCV value.

The upper limit of MFCV values was set at 8 m s^{-1} , based on physiological limits. Three subjects were excluded from SEMG analysis since their MFCVs exceeded this value at least three times. Besides, only one measurement showed such a high MFCV value.

Significance

For all analyses, an observation was regarded significant when $p \leq 0.05$.

Results

Force

Fig. 4.2 shows a typical example of both voluntary and stimulated forces. For the whole group of subjects, during the 2 min of sustained MVC, voluntary force declined significantly from 214.2 (80.1 SD) N to 79.6 (29.8) N [38.2 (7.8)% of initial MVC] (Fig. 4.3A). The decrease of the voluntary force in the first minute exceeded that in the second minute.

Force responses decreased significantly from 14.8 (5.9) N before, to 6.8 (3.5) N [45.0 (15.4)% of the initial stimulated force] after sustained MVC, so from that perspective peripheral fatigue was concluded to be responsible for a force decrease to 45.0 (15.4)%.

The initial and final force responses showed a significant increase of duration from 125.1 (9.6) ms to 211.2 (40.8) ms [169.1 (31.7)% of initial duration], caused by both significantly reduced maximal contraction [from 1.03 (0.21)% ms^{-1} to 0.81 (0.12)% ms^{-1}] and relaxation rates [from 0.60 (0.11)% ms^{-1} to 0.35 (0.07)% ms^{-1}].

CAF showed a significant increase during 2-min sustained MVC. This was most obvious when CAF was expressed by the first method (Fig. 4.3B). Calculated via this method, CAF_1 was found to increase from 18.1 (15.2)% after 15 s to 39.8 (39.9)% after 2-min sustained contraction. When CAF was expressed by the second method (CAF_2) values from 16.9 (13.6)% to 29.0 (21.1)% were found respectively.

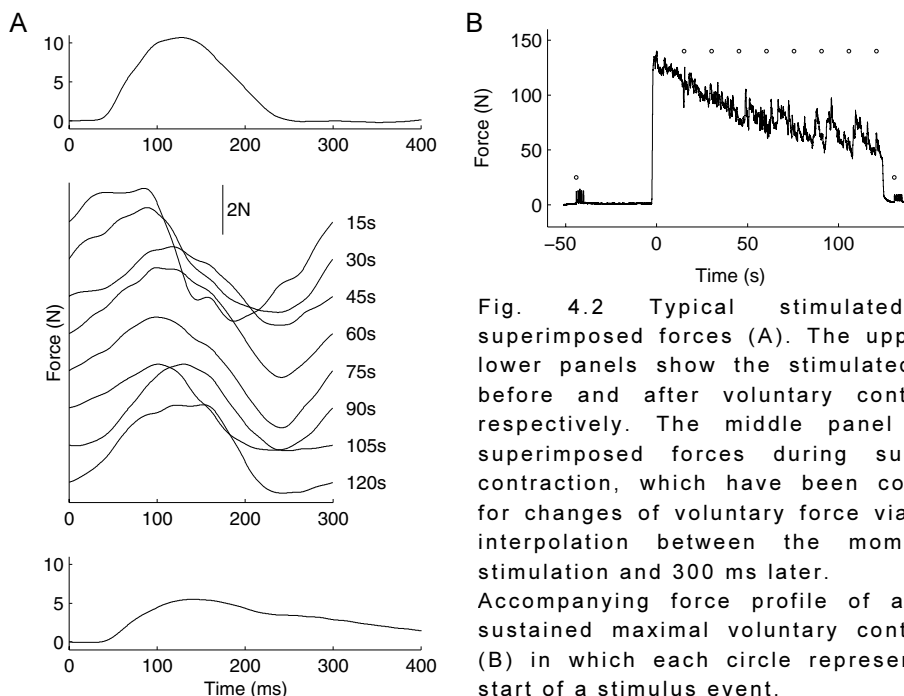


Fig. 4.2 Typical stimulated and superimposed forces (A). The upper and lower panels show the stimulated force before and after voluntary contraction respectively. The middle panel shows superimposed forces during sustained contraction, which have been corrected for changes of voluntary force via linear interpolation between the moment of stimulation and 300 ms later. Accompanying force profile of a 2-min sustained maximal voluntary contraction (B) in which each circle represents the start of a stimulus event.

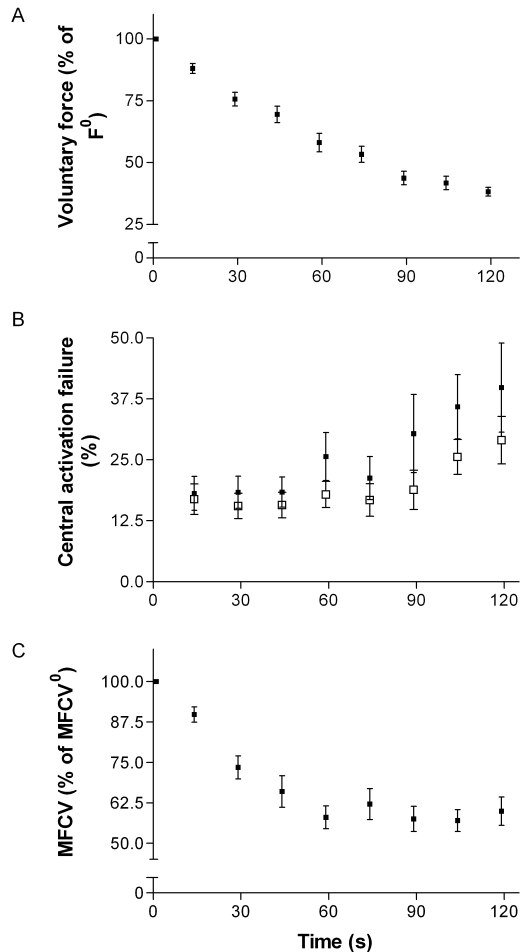


Fig. 4.3 Voluntary force decline, increase of central activation failure (CAF) and decrease of muscle fibre conduction velocity (MFCV) during a 2-min sustained maximal voluntary contraction. Force is represented relatively to MVC values (A). CAF is expressed according to two different methods: as the size of the superimposed force response relative to the voluntary force just before stimulation (CAF_1; closed squares), and as the size of the superimposed force response relative to the estimated maximal force response obtained via linear interpolation between the initial and final force response at rest (CAF_2; open squares) (B). MFCV clearly decreases during the first 60 s, but levels off in the last period of contraction (C). All values are means (SEM). For voluntary force and CAF $n = 19$, for MFCV $n = 16$.

It should be noted that values of CAF revealed much variability between subjects. While some subjects showed a clear increase, others showed no increase or even a decrease of CAF.

SEMG

MFCV showed a mean decline from $5.0 (0.9) \text{ m s}^{-1}$ directly after the start of 2-min MVC to $2.9 (1.0) \text{ m s}^{-1}$ at the end [59.9 (15.9)% of the initial value]. This decline was fully realized during the first minute, while MFCV stayed constant during the last minute of contraction (Fig. 4.3C).

Discussion

The present study has shown that peripheral and central fatigue do not change in parallel in a sustained 2-min MVC of the biceps brachii. During the first minute the decline of voluntary force can be explained almost exclusively by peripheral factors. After about 1 min, however, peripheral fatigue levels off. Then, the further decrease of voluntary force can almost totally be attributed to central fatigue.

Our method does not distinguish between force produced by the biceps brachii and that produced by other elbow flexors. Although the forearm was supinated, which favours the use of biceps brachii, additional activity of other muscles cannot be excluded. For the quantification of central fatigue only biceps brachii has been stimulated. This is supported by Allen et al.⁴, who reported no differences in the amount of central fatigue between studies stimulating just the biceps brachii and studies additionally stimulating brachioradialis.

Loss of voluntary force

The influence of both fatigue modalities resulted in an MVC after a 2-min sustained contraction which was 38.2% of the initial value. The absolute amount of force loss was largest during the first minute. The force curve's shape was similar to that described by Gandevia et al.⁴⁹, who also investigated 2-min sustained MVC of the biceps brachii, and those of others describing different periods of sustained MVC of the same muscle^{113,186}.

Peripheral fatigue

In this study, force responses resulted from trains of five stimuli. Therefore, force responses were intermediate between twitch and tetanic force responses. The choice of this stimulus protocol was based on a pilot study which showed that the force elicited by five stimuli was more than twice as high as a twitch response and more than half the response to a train of 20 stimuli. We therefore considered the behaviour of force responses to be comparable to tetanic contractions, while they were not so uncomfortable that they influenced subjects' voluntary performance.

The significant difference in amplitudes of the force responses before and after the fatiguing contractions in our experiment suggests a large peripheral contribution to fatigue: peripheral fatigue accounted for a force loss to 45.0%, compared to a total voluntary force loss to 38.2%. This implies that 89.0% $[(100-45.0)/(100-38.2)]$ of the force loss can be accredited to peripheral changes. The changes in the contractile properties and the metabolic environment are also expressed by the increase of duration of the stimulated forces, the decreases of the rates of contraction and relaxation and the slowing down of muscle fibre conduction during sustained MVC.

A large contribution of peripheral factors was also found by Gandevia et al.⁴⁹ after 3-min sustained MVC, who reported that voluntary force decreased to 25.9%, while stimulated force decreased to 29.5%. For the ankle dorsiflexors, Kent-Braun⁷⁸ reported that about 80% of the loss of voluntary force during a 4-min sustained contraction could be attributed to peripheral factors.

Assuming that the changes in MFCV reflect the metabolic situation of the muscle^{16,29,97,105}, it is evident from our data that this strongly worsens in the first part of the exercise. In the last part of the contraction no further changes of the intra-muscular situation occurs. Using magnetic resonance spectroscopy, Kent-Braun⁷⁸ showed the same pattern for changes in metabolites for the ankle dorsiflexors. In the literature, at the end of a 65-s sustained MVC of the biceps brachii an increase of MFCV has been shown¹⁸⁶. Experimental evidence indicated that this was because the declining force allows partial restoration of the blood flow.

One could argue that changes of MFCV may be caused by changes in the motor unit recruitment pattern (e.g. by derecruiting the fast conducting type II fibres), which has a central origin. However, based on Zwarts et al.¹⁸⁹, it does not seem likely that the MFCV decline caused by central factors exceeds 0.5 m s^{-1} , where we found a total decline of 2.1 m s^{-1} . Besides, the larger part of the decline was found in the first minute of the sustained contraction, where no central activation changes were seen. Thus, peripheral factors lead to a decrease of voluntary force especially in the first minute of contraction. Then, the decline of voluntary force

continues although peripheral components stabilize. This ongoing loss of voluntary force can be explained by the increased CAF during this period (see Fig. 4.3B and below).

Central fatigue

The present study is the first to report the amount of force loss in biceps brachii because of central activation failure during a sustained contraction. Most earlier work was limited to values at the beginning and end of a sustained contraction^{78,80}. Gandevia et al.⁴⁹ did present a study with data measured during the contraction, but their method of data presentation did not easily allow interpretation in terms of the amount of force lost. Thomas et al.¹⁶⁸ showed the amount of CAF in tibialis anterior and first dorsal interosseus muscles during long sustained maximal voluntary contractions.

The earlier studies showed smaller amounts of central fatigue. Since central activation is known to differ between muscles, only a true comparison can be made with other studies investigating biceps brachii. Investigating five healthy subjects during short maximal contractions in several sessions, Allen et al.⁴ presented CAFs of the same muscle between 0 and 22%. Gandevia et al.⁴⁹, who also studied sustained maximal contraction of biceps brachii, found mean values of 0.7% at the beginning and 9.3% after 3 min sustained MVC in six healthy subjects. Why these values are smaller than the ones showed in the present study is unclear. However, because inter-subject differences are large, confidence intervals still show overlap.

Using superimposed force responses to estimate the amount of failure of central drive during the fatiguing contraction was complicated by the fact that peripheral fatigue caused a decrease of the maximally possible force response. This means that "the ruler to measure the central fatigue changed length during the contraction". To compensate for this disturbing influence of peripheral fatigue, we normalized the superimposed force response: (1) by comparing it with the actual voluntary force and (2) by comparing it with the estimated linearly interpolated stimulated force.

Both methods resulted in a significant increase of CAF during sustained MVC, especially in the last minute (Fig. 4.3B). During the first minute, central activation was submaximal, but only peripheral fatigue contributed to the actual decline of voluntary force. In the last minute, central fatigue was responsible for a further decrease of MVC. It is interesting to discuss the possible advantages and disadvantages of the two different methods used to calculate CAF.

In the first method, which was used by Thomas et al.¹⁶⁸, a superimposed force response is compared with the actual voluntary force left in spite of the fatigue that has already occurred. However, both peripheral and central factors have influenced this voluntary force. Therefore, the correction made in this way is not purely a correction for force loss caused by peripheral factors, but is also influenced by CAF itself. This means that the first method will result in an over-estimation of CAF. The size of this over-estimation increases with increasing CAF.

The second method, which uses linear interpolation between the initial and final force responses, avoids this problem. Interpolation allows us to estimate force responses which are only influenced by peripheral fatigue and which would have been obtained at an arbitrary moment during the fatiguing contraction. However, as concluded above from MFCV changes, in fact peripheral fatigue appears not to increase linearly throughout 2-min sustained contraction. Therefore, apart from the moments at the beginning and at the end of contraction, CAF₂ most probably uses an underestimation of peripheral fatigue during the whole contraction. This means that the force response superimposed on MVC is being compared to an estimated force response that is higher than it actually should be, leading to an underestimation of CAF₂. This underestimation must be highest after about 1 min of contraction, since then the difference between the peripheral fatigue estimated by linear interpolation and the actual peripheral fatigue seems largest. However, especially at the beginning and at the end of contraction the error of CAF₂ will be small, while the error of CAF₁ increases over time.

In conclusion, expressing CAF by the second method appears to give the most valid measure of central fatigue during a sustained MVC. Using this method, it was found that after 15 s of sustained

MVC CAF was 16.9 (13.6)%, which increased by 12.1% to 29.0 (21.1)% at the end of the contraction. Together with the peripheral fatigue which already accounted for 89.0%, this 12.1% increase of CAF clearly explained the total loss of force during a 2-min sustained contraction.

As already mentioned above, in the second method of calculating CAF it was assumed that peripheral fatigue would develop linearly. However, from MFCV measurements it was concluded that the course of peripheral fatigue was more complex. Therefore, we are currently investigating whether MFCV can be used directly to quantify the amount of peripheral fatigue during a sustained contraction. Then, central fatigue could be estimated more precisely.

Conclusions

Expressing CAF by comparing the actual superimposed force response with an estimated force response only influenced by peripheral factors gives the most reliable quantification of central fatigue. In this way, we were able to determine the relative contributions of peripheral and central factors to fatigue during a sustained contraction. It can be concluded that in healthy subjects peripheral fatigue dominates, but central factors become more prominent, during longer sustained isometric contractions. This sequence makes sense, because in the first part of the contraction the output of the muscle is highest, combined with a high metabolic demand and occluded blood flow, resulting in maximal demands on the muscle. In the second half of the contraction, it seems that the continuous and repetitive firing of neurons accompanying the central command is increasingly difficult to maintain. The precise neurological level(s) at which this CAF occurs still has to be determined. In this respect it would be interesting to see how this interplay between central and peripheral factors ensues in different types of contraction. Future studies including different patient populations may reveal the impact of both aspects of fatigue in several diseases.

Chapter 5

Determining central activation failure and peripheral fatigue in the course of sustained maximal voluntary contractions: a model based approach

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Abstract

In the study of fatigue, several methods have been used to calculate the development of central activation failure (CAF) and peripheral fatigue (PF) in the course of a sustained maximal voluntary contraction (MVC). This paper presents a model, which enables simultaneous determination of CAF and PF during sustained MVC, by only using force registration and superimposed electrical stimulation. In the model, we explicitly use the assumption, which is virtually always made implicitly in earlier studies, that a constant relative fraction of maximal possible force is activated by the electrical stimulation. That fraction can be determined at the start and at the end of a sustained MVC. The model shows that in the course of a sustained MVC, CAF can be calculated by merely using (i) this fraction, (ii) the amplitudes of the superimposed force responses to stimulation and (iii) the course of voluntary force. After CAF quantification, the development of PF during MVC becomes available as well.

The present study first examines the model assumption with data of sustained MVCs of variable durations on six healthy subjects. Subsequently, it shows CAF values in a group of 27 healthy subjects determined both with the model and with a method of linear interpolation for PF estimation. Model based CAF values were significantly higher during, but not at the start and at the end of a 2-min sustained MVC. Next to a well justified CAF determination, the model has the advantage of simultaneously quantifying PF, which was not possible with the previous methods.

Introduction

Physiological fatigue is usually defined as a loss of maximum force-generating capacity⁷⁸. On the basis of the site of the origin of force loss, causes of fatigue can be divided into peripheral and central factors, whereby neuromuscular junctions and muscle tissue are regarded as the peripheral sites and the "higher" systems as the central sites. During a sustained maximal voluntary contraction (MVC), both factors influence the course of voluntary force. Separating the contributions of peripheral and central factors to a force decline is complicated.

Peripheral fatigue (PF) has generally been measured by comparing the force responses to electrical stimulation before and after a fatiguing exercise. Quantification of PF expressed in relative force decline during a sustained contraction has not been possible.

To determine the contribution of central factors to fatigue, several studies have used variants of the twitch interpolation technique: a combination of MVC and electrical nerve stimulation⁴⁸. Force responses to stimuli superimposed during sustained MVC are used as indicators of the amount of central activation failure (CAF). The amplitude of these superimposed force responses, however, is not only influenced by the amount of central activation, but also by the current amount of PF⁹³. Some authors neglected this disturbing factor^{152,153,168}, whereas others developed methods to avoid or handle it^{13,23,80,82}. In earlier studies by our group^{140,141}, we assumed PF to induce a linearly declining force during sustained MVC. Such assumption, however, is not based on physiological evidence.

In this paper we deduce a model to simultaneously calculate CAF and PF during a sustained MVC. Electrical stimulation during rest usually activates only part of the muscle tissue. All studies determining CAF implicitly assume that this force response is representative for the force response that would have been obtained if the total muscle tissue were activated. Indeed, Bigland-Ritchie and coworkers¹¹ describe how in the unfatigued state the size of superimposed force responses to single twitches responds

nearly linearly to the performed level of MVC. The contribution of PF to the force response to stimulation is thus assumed to be proportional to its contribution to total muscle force. If this assumption is recognized more explicitly, it can be used to determine the contribution of both central and peripheral factors to fatigue during a sustained MVC.

The linear approach and the newly presented method are evaluated with experimental MVCs of variable duration. In addition, CAF values determined with both methods from 2-min sustained MVCs will be compared.

Materials and methods

Model development

During a sustained MVC with additional electrical stimulation (Fig. 5.1), CAF at time point t can be determined by

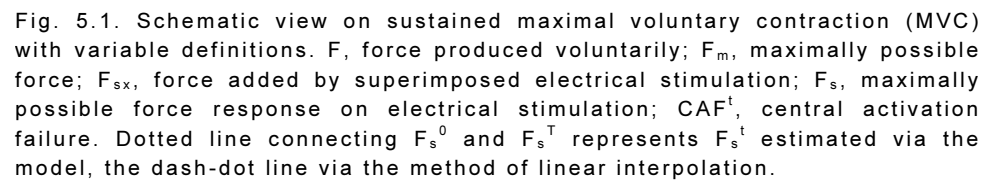
$$CAF^t = \frac{F_{sx}^t}{F_s^t} \quad (1).$$

CAF^t can vary between 0 and 1. It represents the fraction of maximal possible force that is not activated voluntarily. A higher value indicates a larger failure of central activation. F_{sx}^t represents the amplitude of the force added by superimposed electrical stimulation (Fig. 5.1). F_s^t is the maximally possible force response on electrical stimulation. It would occur if CAF^t were 1, in case voluntary central activation was absent (i.e., during rest).

F_{sx}^t can be measured during the exercise, but obviously there is no possibility to directly measure F_s^t . The essence of CAF determination is to estimate F_s^t despite this inaccessibility.

All studies into CAF implicitly assume that the relative fraction of maximally possible muscle force that can be produced with the specific stimulation parameters is constant. With β as this relative fraction, this assumption can be written as

$$F_s^t = \beta^t \cdot F_m^t \text{ with } \beta^t = \beta = \text{constant}$$



At first sight, explicitly stating this assumption seems not to be very helpful in the estimation of F_s^t , because neither β nor F_m^t can be measured directly during ongoing exercise. However, the values of $\beta^t = \beta$ and F_m^t can be determined. Because we assume β to be independent of time, determining β^t at any time t should be sufficient. In practice, it can be calculated at two moments in time, namely directly at the start (β^0) and at the end (β^T) of the contraction.

$$\beta^0 = \frac{F_s^b}{F_m^0} \quad (2).$$

F_s^b (i.e. the force response to an electrical stimulus during rest before MVC, Fig. 5.1) can be measured directly.

We know that:

$$F^t = (1 - CAF^t) \cdot F_m^t \quad (3),$$

in which F^t is the force voluntarily produced (Fig. 5.1), and therefore at the start of exercise:

$$F_m^0 = \frac{F^0}{1 - CAF^0} \quad (3a).$$

Since

$$CAF^0 = \frac{F_{sx}^0}{F_s^0} \quad (1a),$$

equation (3a) can be rewritten as

$$F_m^0 = \frac{F^0}{1 - F_{sx}^0 / F_s^0} \quad (4).$$

F_s^0 is supposed to be equal to F_s^b (Fig. 5.1). Combining equations (2) and (4) and substituting F_s^b for F_s^0 results in

$$\beta^0 = \frac{F_s^b}{F^0 / (1 - F_{sx}^0 / F_s^b)} = \frac{F_s^b}{F^0} \cdot \left(1 - \frac{F_{sx}^0}{F_s^b} \right) = \frac{F_s^b}{F^0} - \frac{F_s^b \cdot F_{sx}^0}{F^0 \cdot F_s^b} \quad (5).$$

This can be rewritten as

$$\beta^0 = \frac{F_s^b \cdot F_s^b}{F^0 \cdot F_s^b} - \frac{F_s^b \cdot F_{sx}^0}{F^0 \cdot F_s^b} = \frac{F_s^b \cdot F_s^b - F_s^b \cdot F_{sx}^0}{F^0 \cdot F_s^b} = \frac{F_s^b - F_{sx}^0}{F^0} \quad (6).$$

In words: the denominator F^0 represents the maximal voluntary force, which is the maximal possible force (F_m^0) minus the force 'lost' because of the presence of central activation failure ($CAF^0 \cdot F_m^0$, see Fig. 5.1). The numerator represents the maximal possible stimulated force minus the amount of force that can be added to F^0 by electrical stimulation because of CAF. Via equation (6), β^0 can be determined using three variables that can all be measured directly.

Similarly, β^T can be determined (Fig. 5.1) via

$$\beta^T = \frac{F_s^e - F_{sx}^T}{F^T} \quad (6a).$$

Now that we know how β can be calculated at time 0 and time T , we will derive the consequences for the CAF^t determination.

Combining the explicit assumption with equation 1 leads to

$$CAF^t = \frac{F_{sx}^t}{\beta \cdot F_m^t} \quad (7).$$

Since

$$F_m^t = F^t + F_m^t \cdot CAF^t \quad (\text{see Fig. 5.1})$$

equation (7) can be rewritten as

$$CAF^t = \frac{F_{sx}^t}{\beta \cdot (F^t + F_m^t \cdot CAF^t)} \quad (7a).$$

Combining equation (7a) with equation (1) gives

$$CAF^t = \frac{F_{sx}^t}{\beta \cdot (F^t + F_m^t \cdot F_{sx}^t / F_s^t)} = \frac{F_{sx}^t}{\beta \cdot (F^t + F_{sx}^t \cdot F_m^t / F_s^t)} \quad (7b).$$

With the use of the explicit assumption $F_s^t = \beta^t \cdot F_m^t$, this results in

$$CAF^t = \frac{F_{sx}^t}{\beta \cdot (F^t + F_{sx}^t \cdot 1/\beta)} \quad (8).$$

Having calculated values for CAF and β , PF during MVC can be determined:

$$PF^t = 1 - \frac{F_s^t}{F_s^b} = 1 - \frac{\beta \cdot F_m^t}{F_s^b} = 1 - \frac{\beta \cdot F^t / (1 - CAF^t)}{F_s^b} \quad (9).$$

After a last simplification in writing, equations (8) and (9) result in the following equations to determine CAF and PF:

$$CAF^t = \frac{F_{sx}^t}{\beta \cdot F^t + F_{sx}^t} \quad (8a),$$

and

$$PF^t = 1 - \frac{\beta \cdot F^t}{(1 - CAF^t) \cdot F_s^b} \quad (9a).$$

In fact, to determine CAF^t , the amplitude of F_s^t (see equation (1) and Fig. 5.1) is now estimated by $\beta \cdot F^t + F_{sx}^t$. When β has been determined as described above with equations (6) and/or (6a), the

manageable descriptions (8a) and (9a) can be used to calculate CAF and PF values during a sustained MVC at any moment at which electrical stimulation is applied.

Experimental procedures

Experiment 1

The first experiment was designed to test the validity of the assumption of a constant β over time. In addition, it provides the possibility to test if PF can be assumed to develop linearly, as supposed in our former studies. This is also relevant because CAF values obtained with both methods will be compared in Experiment 2.

Six healthy subjects (age 22.4 (SD 1.5); 5 women, 1 man) were recruited for this experiment. They gave their informed consent before the first experiment. The protocol was approved by the local ethics committee "Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen". The experimental setup has been described in detail elsewhere^{140,141}. In our former studies, subjects made a single 2-min sustained MVC of the elbow flexor muscles. In the present experiment, trials of 15, 30, 45, ..., and 105s MVC (8 levels) were also made.

In short, subjects were instructed to make a sustained MVC of their biceps brachii muscle. Before and directly after contraction, a stimulus event (described below) was applied to the relaxed muscle at the endplate region. During MVC, stimulus events were applied every 15 s, starting directly after the start of contraction. The last stimulus event was given just before cessation of the voluntary contraction. A stimulus event (Fig. 4.1) consisted of five times a five-pulse 100-Hz train (duration 40 ms). Pulse duration was 100 μ s. The average of the five responses to such a short train is referred to as 'the force response' and is used for analysis. During voluntary contraction the intertrain interval was 300 ms; during rest the intertrain interval was 1,000 ms. Pilot experiments had shown that these intertrain intervals were appropriate to avoid fusion of the single force responses. Before the start of the protocol, the location of the motor points was determined. Then the current was increased until the force did not rise anymore. This intensity was

used in all stimulus events. The initial stimulus event was not preceded by a short voluntary contraction, because pilot experiments showed that potentiation did not occur with this type of stimulus event.

The subsequent trials were separated at least 2 days, and the eight trials had a random order. Subjects were not informed about the duration of the contraction, but they knew it would be in between 15 s and 2 min. To keep intertrial variability as low as possible, for every subject chair height and ergometer settings were kept constant. The location of the electrodes for stimulation stayed marked on the subjects' arms during the period of the complete set of experiments.

To test the assumption of a constant β , this variable was determined both at the start (β^0) and at the end (β^t ; $t = 15, 30, \dots, 120$ s) of every trial. For each individual, β^t / β^0 was plotted vs. t . Least-squares linear regression analysis tested slope ($\neq 0$) significance. The same procedure was performed on the averaged data from the six subjects.

To test the validity of the assumption of a linear increase of PF, we tested whether F_s^t declined linearly with time ($t = 15, 30, \dots, 120$ s) during MVC. To reduce intertrial variability, relative values (F_s^t / F_s^b) were calculated from data within each trial. For each individual, a linear ($F_s^t / F_s^b = q + r \cdot t$), a second-order polynomial ($F_s^t / F_s^b = q + r \cdot t + s \cdot t^2$), an exponential ($F_s^t / F_s^b = q + r \cdot e^{st}$) and a power function ($F_s^t / F_s^b = q + r \cdot t^s$) were fit via the least-squares technique. F tests were used to determine whether one or more of the three-parameter functions (exponential, second-order polynomial and power) were better than the two-parameter function (linear). The same analysis was done on the averaged data of all subjects. R^2 of the linear fit was also determined.

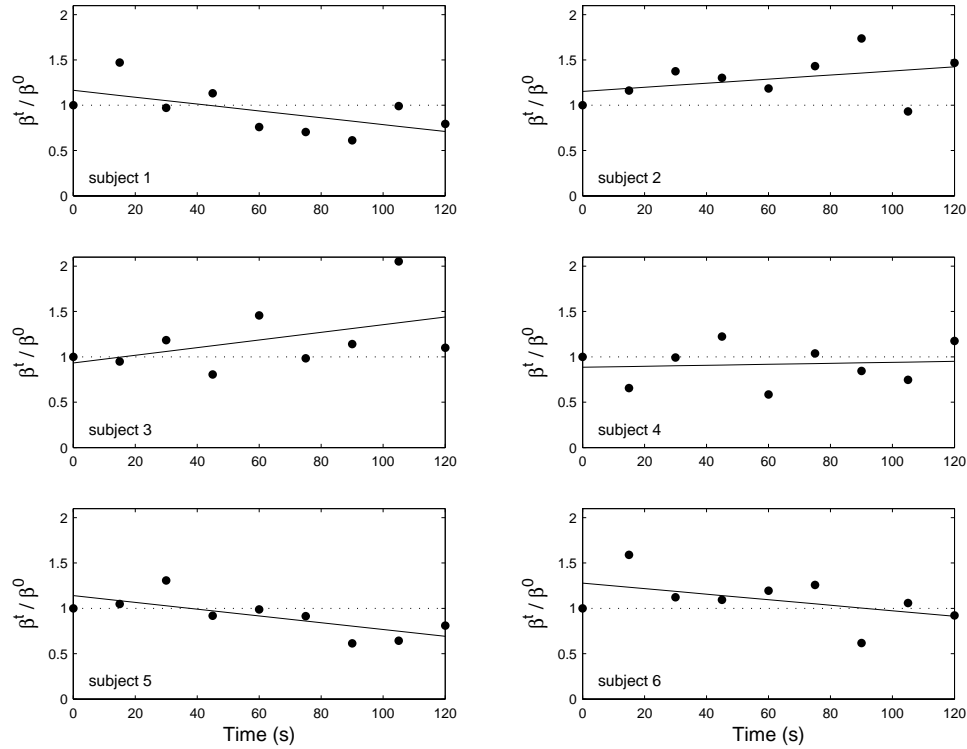


Fig. 5.2. Relative values of β^t at the end of sustained MVCs of variable durations ($t = 0, 15, 30, \dots, 120$ s) as a fraction of the value of β at $t = 0$ s. β represents the fraction of the muscle that is activated by electrical stimulation, so a change of β^t / β^0 to values not equal 1 would indicate a change of β with fatigue. Each panel shows an individual subject. Solid lines show linear fits. Except for subject 5, slopes of these fits do not significantly deviate from 0. In all subjects, the point of cross sectioning the y-axis does not significantly deviate from 1.

Experiment 2

Both the linear interpolation method and the newly presented method were applied on data of a 2-min sustained MVC with electrical stimulation. Therefore, data of 27 healthy subjects (age: 39.8 (SD 14.3); 15 women, 12 men) were used. The data from some of these subjects were presented in our earlier studies^{140,141}. The protocol was the same as described for experiment 1.

Both β^0 and β^T were determined via equations (6) and (6a), respectively. Values were compared with a paired-samples t-test.

Least-squares linear regression determined the relation between β^0 and β^T .

For computing CAF and PF via the model, for each subject the mean of β^0 and β^T was used in equations (8a) and (9a). Possible differences between CAF values determined with the model and the method of linear interpolation were tested with multiple paired-samples t-tests. The model provided PF values at any moment during the contraction at which a stimulus event was given. The linear interpolation method only uses information about peripheral fatigue after finishing the 2-min sustained contractions. Obviously, the linear interpolation also gives an estimate for PF at any moment during contraction. PF values obtained by both methods during sustained 2-min MVC were compared with multiple paired t-tests.

Statistics

Differences were regarded significant if $p < 0.05$. Regression analyses and paired-samples t-tests were performed with the Statistical Package for the Social Sciences (SPSS) 12.0.1; F tests were done with Matlab 6.5 (The MathWorks).

Results

Experiment 1

Data of each individual collected from the eight trials of MVC of variable duration are presented in Fig. 5.2 and 5.3.

Fig. 5.2 shows the course of β^t/β^0 . In all but one subject, the slope of the linear fit was not significantly different from zero. In subject 5, the slope was negative ($p = 0.027$). Mean R^2 of the linear fit was 0.25 (SD 0.18), also indicating the lack of a linear trend with time. When all subjects were averaged, $\beta^t/\beta^0 = q + r \cdot t$ fitted best with $q = 1.09$ and $r = -0.068$. If β^t/β^0 had been perfectly constant, q and r would be 1 and 0, respectively. The 95% confidence interval of q was 0.98 – 1.20; the 95% confidence interval of r was -0.221 to $+0.085$. Thus $\beta^t/\beta^0 = 1 + 0 \cdot t$ did not describe the relation significantly worse than the best fit.

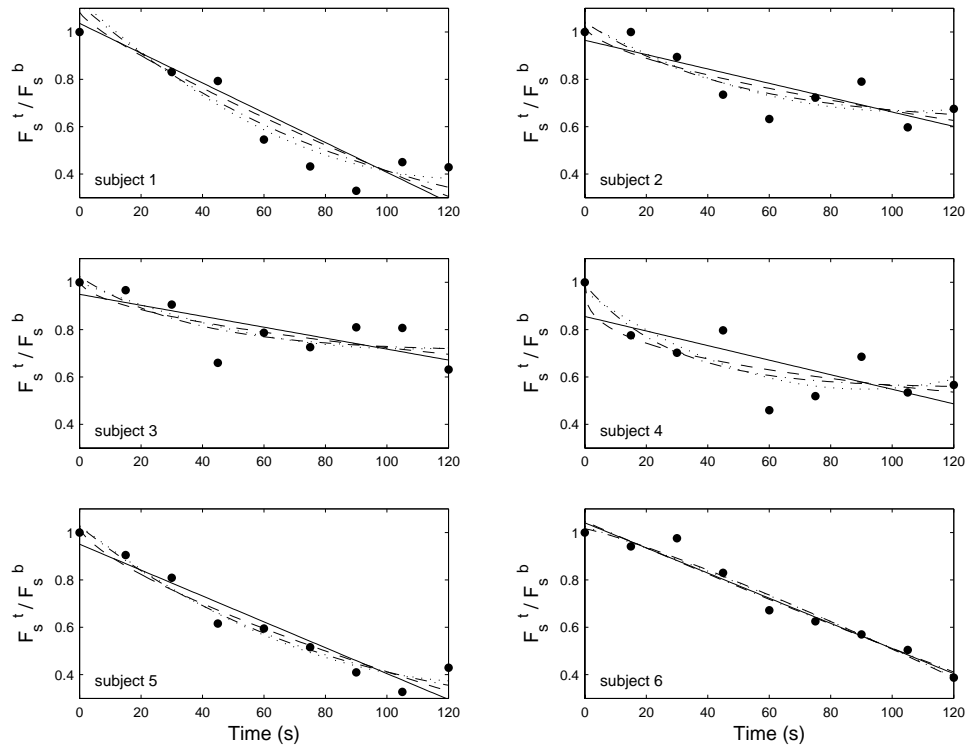


Fig. 5.3. Relative amplitudes of F_s^t (Fig. 5.1) measured at the end of sustained MVCs of variable durations. Black dots show the amplitudes of the final force responses during rest after the MVCs as a fraction of the amplitudes of the initial force responses. Each panel presents an individual subject. Solid lines represent linear fits; dotted lines, second order polynomial fits; dash-dot lines, exponential fits; dashed lines, power fits. In all subjects but subject 5 the 3-parameter functions were not significantly better than the linear one. In that subject, both a second-order polynomial and an exponential fit did significantly better than a linear fit.

With respect to PF, in five of the six individual subjects, neither a second-order polynomial nor an exponential or power function described its course significantly better than the linear function (Fig. 5.3). Mean R^2 of the linear fit was 0.75 (SD 0.18). In one subject (subject 5) both a second-order polynomial and an exponential fit were significantly better than a linear fit ($p = 0.025$ and $p = 0.044$, respectively). Averaged data of the six subjects were best described by a second order polynomial fit

$[F_s^t/F_s^b = 1.03 + (-7.98 \cdot 10^{-3}) \cdot t + (3.11 \cdot 10^{-5}) \cdot t^2; p = 0.012]$. R^2 of the linear fit $[F_s^t/F_s^b = 0.966 + (-4.25 \cdot 10^{-3}) \cdot t]$ was 0.92.

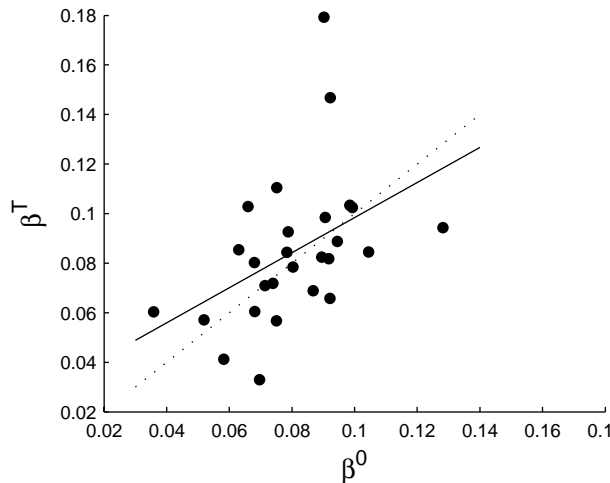


Fig. 5.4. Correlation between β^T and β^0 . These variables represent the fraction of the muscle that can be activated by electrical stimulation at the end and the start of a 2-min sustained MVC, respectively. The least-squares method determined the best data description to be $\beta^T = 0.028 + 0.708\beta^0$ (solid line). However, $\beta^T = \beta^0$ (dashed line) did not describe the data significantly worse.

Experiment 2

In the group of 27 subjects who made a 2-min sustained MVC, a paired samples t-test showed that β^T was not significantly different from β^0 . Values of β^0 and β^T correlated significantly ($p = 0.022$, $R = 0.44$; Fig. 5.4). Data presented in Fig. 5.4 were best described by $\beta^T = q + r \cdot \beta^0$ with $q = 0.028$, and $r = 0.708$. The 95% confidence intervals of q and r were -0.022 to $+0.077$ and $0.112 - 1.305$, respectively, and thus included 0 and 1. This means that, within a considerable scatter, $\beta^T = \beta^0$ can be considered valid.

CAF values during a 2-min sustained MVC calculated via the two different methods are presented in Fig. 5.5. Except for CAF at the start and at the end of sustained MVC, CAF determined with the model was significantly higher than with the linear method.

Fig. 5.6 shows values of PF during the sustained MVC. As is obvious, PF develops linearly via the method of linear interpolation. The curved line shows PF calculated according to the presented model. Except for PF at the start and at the end of sustained MVC, PF was significantly higher if estimated via the model than using the linear method.

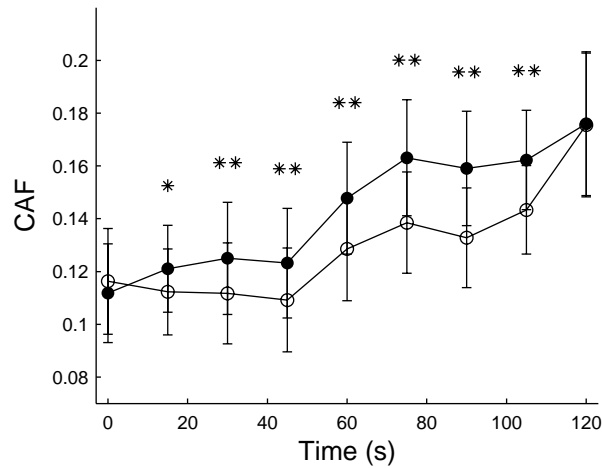


Fig. 5.5. CAF of 27 subjects calculated via the method of linear interpolation (open circles) and the model (closed circles). Values are means \pm SEs. Significant differences: * $P < 0.05$ and ** $P < 0.01$.

Discussion

In this paper we proposed a model to determine CAF during sustained MVC. It enables simultaneous unbiased calculation of CAF and PF from force recordings at any moment during the contraction, provided that superimposed electrical stimulation is given just after the start of, just before the end of, and at the moments of interest during sustained MVC.

Several studies have determined CAF at the start and at the end of a sustained contraction by comparing the decline in voluntary force with the decline in tetanic force during rest^{e.g. 13,78,168}. Other studies have compared the superimposed force response at the start of contraction with the force response during rest before starting exercise, while the superimposed force response at the end of contraction was compared with a force response during rest just after finishing exercise²³. To enable CAF determination at intermediate points in time during a sustained contraction, in our earlier studies we assumed a linear PF increase during sustained MVC^{140,141}. In this way, the force response of the muscle in rest, F_s^t , was assumed to be known at any moment in time, facilitating CAF estimation. However, other measures for PF, such as muscle fiber conduction velocity and pH values, appeared to indicate a nonlinear increase of PF^{78,140,166}. The present study shows that in the particular case of a 2-min sustained MVC of the elbow flexor muscles, linearity cannot be rejected; a linear function did not

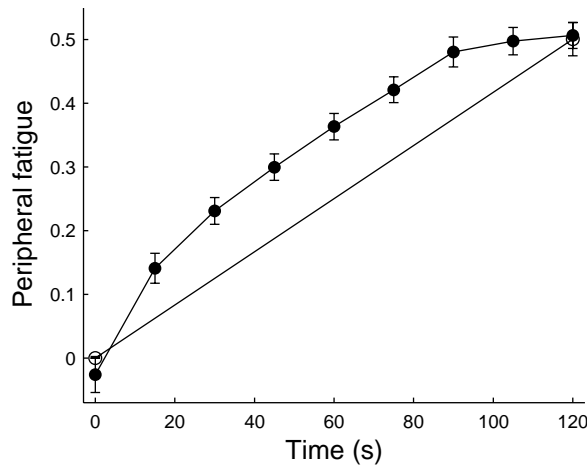


Fig. 5.6. Peripheral fatigue of 27 subjects during sustained MVC. According to the linear method, peripheral fatigue develops linearly (straight line). The model enables the calculation of peripheral fatigue during sustained MVC (closed circles). Values are means \pm SEs.

describe the data significantly worse than more complex functions in five out of six subjects. However, in one individual and also when data of all subjects were averaged, a second-order polynomial was more accurate. We expect this kind of nonlinearity to be more prominent if sustained contractions of longer durations or at lower force levels are made.

An earlier method related the size of the superimposed force responses to the actual MVC^{49,82,151}. In this case, to determine CAF, the implicit assumption was made that the decline of MVC is fully caused by peripheral factors. The decline of MVC caused by central fatigue, the variable to be estimated, was neglected, which is principally inconsistent and disturbs the calculation of CAF when it is significantly different from zero. A better method was introduced by Kent-Braun^{78,79} and Kent-Braun and Le Blanc⁸⁰, and also used by Nybo and Nielsen¹²⁰ and Stackhouse et al.¹⁶⁰. They calculated central activation as MVC divided by the total muscle force, where the total muscle force is the sum of MVC plus force from superimposed electrical stimulation. In general, however, the value of the added force and thus the total force depends on the stimulus given (duration, frequency, amplitude), and higher CAF values will be obtained when the stimulus is able to activate a larger part of the muscle more strongly^{68,155}. This is actually illustrated by Stackhouse and coworkers¹⁶⁰. They determined a so-called central activation ratio during nonfatiguing contractions at defined percentages of maximum voluntary effort using different

stimulus trains. The results reported higher ratios than anticipated based on the effort level, an effect that was stronger when the stimulus train resulted in a lower electrically elicited force during rest¹⁶⁰.

In the mathematical model, the actual value of β theoretically does not influence the determined value of CAF. To obtain a reproducible result, stimulation should be preferentially supramaximal, although activation of antagonists should be avoided¹⁵⁵. If the stimulus event is such that a preceding MVC potentiates the force response, care must be taken that the initial rest twitch is also potentiated⁴⁸. Shield and Zhou¹⁵⁵ discuss the advantages and disadvantages of different types of stimulus events.

Our results showed that the assumption of a constant relative fraction (β) of maximally possible force (F_m^t) being activated by electrical stimulation, was reasonable in five of six individual subjects and in the averaged data of these subjects. Likewise, data of 27 healthy subjects showed no significant change of β over 2-min sustained MVC. We do not expect that this relation will change when MVC is being sustained for a longer period.

On the basis of the presented results, both the linear PF development assumption and the new model appear to be defensible on the data of individual subjects in the case of a 2-min sustained MVC of the elbow flexors. On the averaged data, the linear development of PF can already be rejected for this short exercise. So we advise to use the newly presented method in future studies determining the course of CAF during sustained MVCs. First of all, it has the advantage of determining PF simultaneously, which previously was not possible without the use of additional techniques. It can also be argued to be the safer choice because of absence of any assumptions in CAF determination, except for the assumption of a constant β that is implicitly present in almost all methods. Finally, it should be noted that application of the model is not restricted to sustained maximal efforts. Theoretically, it can also be used in protocols using lower force levels or for interrupted contractions.

Chapter 6

Central adaptations during repetitive contractions assessed by the readiness potential

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Submitted

Abstract

Physiological fatigue, a loss of maximal force producing capacity, may originate both from changes at the peripheral and at the central level. The readiness potential (RP) provides a measure to study adaptations to physiological fatigue at the motorcortex. We have studied the RP in the course of repetitive contractions at a high force level.

Fourteen female healthy subjects made repetitive force grip contractions at 70% of their maximal voluntary contraction (MVC) for 30 minutes. Contractions were self-paced and inter-squeeze interval was about 7 s. During the repetitive contractions, the area under the curve of the RP almost doubled at electrode Cz and increased fourfold at electrodes C3' and C4'. The onset of negativity moved forward from 1.5 s to 1.9 s before force onset at Cz and from 1.0 s to 1.6 s and 1.7 s before force onset at C3' and C4', respectively. EMG amplitude and median frequency did not change significantly and MVC after the fatiguing exercise was 93% of MVC before, indicating only little physiological fatigue. The increase of the RP during the repetitive contractions is clearly in excess of the almost absent signs of peripheral fatigue. Because the increase of the RP does not lead to an increased force production, we propose that it is a central adaptation counteracting the decrease of cortical efficiency during repetitive contractions.

Introduction

Physiological fatigue is usually defined as an exercise induced decrease of maximal voluntary force producing capacity. It may originate from changes in the nervous system (central fatigue) and/or in the muscle tissue (peripheral fatigue). Both types of fatigue occur in healthy subjects^{13,49,78,140}.

Central fatigue has been shown at the level of the peripheral nervous system by the method of twitch interpolation. To study fatigue more upstream in the nervous system, magnetic and electrical stimulation at supraspinal sites have been used^{48,165}. These techniques give artificial input into the nervous system and measure the response at the output site by recording the force or the electrical muscle response.

Freude and Ullsperger⁴¹ have introduced the readiness potential (RP) in the study of fatigue. This negative movement-related cortical EEG potential appears over the human scalp about one second or more before a self-paced motor act. It is mainly generated by the supplementary motor area (SMA) and the primary motor cortex (MI)³². In the absence of fatigue, its amplitude is related to the amount of voluntary force^{8,41} and perceived effort¹⁵⁸. It provides a measure to determine changes at the motorcortical level, which I) does not require artificial input and II) measures directly at the level of the motor cortex instead of at the output site. It cannot be used during sustained contractions, but is an especially interesting tool for studying central changes during more natural repetitive contractions.

As far as we know, only two studies describe the change of the RP during a fatigue inducing protocol. Freude and Ullsperger⁴¹ studied the RP during repetitive contractions at three different force levels, Johnston et al.⁷⁴ during repetitive contractions at 70% of the maximal voluntary contraction (MVC). During repetitive voluntary contractions at a high force level the RP increased, which was regarded as a way to compensate for peripheral fatigue^{41,41,74,74}. However, an increase was present also during repetitive contractions at a low voluntary force level⁴¹, when peripheral fatigue is not expected to develop.

The present study was developed to further investigate the behavior of the RP during repetitive contractions at a high force level. It presents EEG, EMG and force data of exercise that induces only little physiological fatigue. In order to avoid varying recovery times during the different stages of the experiment, we chose to use self-paced 7-s intervals, whereas Freude and Ullsperger⁴¹ instructed subjects to squeeze at self-paced irregular intervals of 4 – 10 s. The high force level studied by Freude and Ullsperger⁴¹ was 80% MVC, but not all subjects were able to perform the total series of contractions. Pilot experiments of our group showed that healthy subjects are able to repetitively produce 70% MVC for half an hour. This duration was needed to induce possible central changes and simultaneously enable reliable averaging of the EEG potential. It was the same force level as studied by Johnston et al.⁷⁴. However, in their study contractions were sustained for 5 s, whereas they were short in our study. The shorter contractions lead to less physiological fatigue in our protocol.

Methods

Subjects

Fourteen female healthy volunteers without a history of neurological problems (age 26.6, SD 5.8, range 19-39) participated in this study. All subjects were right-handed, based on self-report. All subjects gave written informed consent. The protocol was approved by the local ethics committee, experiments were performed in accordance with the Declaration of Helsinki.

Experimental setup

Subjects sat on a chair with both forearms comfortably resting horizontally on a table. The right arm was stabilized by means of a vacuum pillow. Isometric handgrip force of the right, semi-supinated forearm was measured with a grip force dynamometer. EEG was continuously recorded from Ag/AgCl electrodes at Cz, C3' (1 cm before C3), C4' (1 cm before C4), Pz, and Fz, according to the international 10-20 system⁷³. In analyses, only Cz, C3' and C4' were used. Linked mastoids were used as references. Impedances

were kept $< 10\text{k}\Omega$. Ag/AgCl electrodes positioned laterally to the right and left eye and directly above and below the left eye recorded bipolar horizontal EOG and vertical EOG, respectively. Surface EMG was recorded bipolarly from the muscle belly of the flexors and extensors of the fingers of the right hand, using NCS2000 disposable self-adhesive electrodes with 1 cm inter-electrode distance. Impedances of EOG and EMG were kept $< 30\text{k}\Omega$.

EEG, EOG and EMG were acquired with a multi-channel bioelectric amplifier (Neurotop 32). Signals were band-pass filtered (EEG and EOG: 0.016 Hz - 70 Hz, EMG: 10 Hz - 70 Hz).

Data was sampled at 250 Hz and fed into a PC running Neuroscan 4.1 Acquire software. Force data was recorded both on the Neuroscan-PC and on a PC with custom made force acquiring software.

Protocol

The experiment started with three initial MVCs, separated by one-minute rest periods. The strongest MVC was used for analysis. Then, the subjects' task was to make a 30-min series of repetitive handgrip contractions to 70% of the maximum MVC. Contractions were self-paced and had to be about seven seconds apart. Subjects were instructed to relax immediately when the target force was reached. Before starting the trial, subjects had a short exercise period requiring low force levels in order to practice on interval timing. Directly at the end of the 30-min series, subjects made three final MVCs quickly following each other to prevent in between recovery. The strongest was used for analysis.

Real-time visual force feedback was provided by means of two adjacent columns of 16 leds each, that were vertically arranged and placed 1.5 m in front of the subjects. During the 30-min series, resolution of force presentation was 1.6% MVC per led. The 70% MVC level was indicated halfway by a horizontal bar beside the respective leds.

Data analysis

The 30-min series of repetitive contractions were divided into five subsequent 6-min periods from which data was averaged. Accuracy

of task performance during the 30-min series was checked by investigating handgrip forces and inter-squeeze intervals.

EEG, EOG and EMG epochs ranging from 3.0 s before to 1.0 s after force onset were collected using Neuroscan 4.1 Edit software. Force onset was defined as the moment at which force exceeded 5% MVC. Baseline EEG and EOG was the average from 3.0 to 2.5 s before force onset. Automatic ocular artifact reduction was done¹⁴⁵ and all epochs were visually inspected to remove major artifacts.

For every subject, mean epochs for the five subsequent periods of six minutes were low-pass filtered at 10 Hz, using Matlab 6.5 (The MathWorks). At electrodes C3', C4' and Cz the onset of the RP was determined visually after randomization of the trials. Earlier studies have recognized several potentials within the RP^{32,33,129,154,159}. However, different authors have used different terms and the exact time intervals of these shorter potentials are not very consistent. Based on Freude and Ullsperger⁴¹, we chose to study four subsequent time intervals within the RP. Areas under the curve were automatically determined at the following intervals: 2.0 – 1.5 s, 1.5 – 1.0 s, 1.0 – 0.5 s and 0.5 – 0.0 s before force onset. Please notice that the term 'period' is used for the 6-min parts of the 30-min series of repetitive contractions, the term 'interval' is used for the 0.5-s parts of the RP. We studied areas under the curves instead of maximal amplitudes in order to reduce the influence of noise in the EEG data.

Median frequencies of the bipolar EMG of both flexors and extensors were determined from force onset to 1.0 s after force onset. Maximum amplitudes were determined from the rectified bipolar EMG.

Statistics

Statistical tests were performed with the Statistical Program for the Social Sciences (SPSS) 12.0. MVCs before and after exercise were compared with a paired samples t-test. To investigate changes over the five subsequent 6-min periods, linear regression was performed in Microsoft Excel 2000. One-sample t-tests determined if slopes or areas deviated from zero. Pearson's correlations were determined between force and EEG slopes. Significance was set at $p \leq 0.05$.

Results

Force and EMG

The initial MVC was 363 (36 SD) N. After the exercise period, MVC had declined significantly to 336 (46) N, which is 92.5 (9.6)% of the initial value ($t = 2.93$, $p = 0.012$).

Subjects made repetitive handgrip contractions at mean force levels between 67.6 (4.0)% and 76.1 (5.8)% of the initial MVC; group mean force level was 72.7%, mean SD 3.8%. Mean inter-squeeze intervals varied between 4.7 (0.7) s and 8.5 (1.9) s; group mean interval was 7.1 s, mean interval SD 1.0 s. Neither mean force (Fig. 6.1), nor variability of the mean force, mean inter-squeeze interval or its variability changed during the five subsequent 6-minute periods. In the final 6-min period, produced force was 78.7 (6.8)% of the final MVC.

Maximum EMG amplitudes (Fig. 6.1 and Table 6.1) and median frequencies of both flexors and extensors (Table 6.1) showed no significant change over the five subsequent 6-min periods. EMG values are relatively low due to the 70Hz low pass filtering, used to avoid aliasing by the sampling rate of 250 Hz.

	0-6 min	6-12 min	12-18 min	18-24 min	24-30 min
maximal amplitude flexors (μV)	159 (101)	143 (77)	143 (81)	142 (73)	140 (70)
maximal amplitude extensors (μV)	170 (96)	166 (109)	157 (85)	155 (87)	153 (85)
median frequency flexors (Hz)	53.4 (2.9)	53.1 (4.1)	53.4 (4.0)	53.8 (3.4)	53.8 (3.7)
median frequency extensors (Hz)	51.4 (5.2)	51.2 (6.0)	50.1 (6.5)	51.6 (5.5)	52.2 (5.6)

Table 6.1. EMG variables (means (SD)) during a 30-min series of repetitive handgrip contractions at 70% MVC. Values do not change significantly.

EEG

Fig. 6.1 shows grand averages of the five subsequent 6-min intervals from the electrodes covering the motor cortex (Cz, C3' and C4'). The onset of RP became significantly earlier in the course of the 30-min series at electrodes C3' and C4' and showed a trend at electrode Cz (C3': $t = 2.33$, $p = 0.037$; C4': $t = 2.36$, $p = 0.035$; Cz: $t = 1.94$, $p = 0.075$). At Cz the onset of negativity was

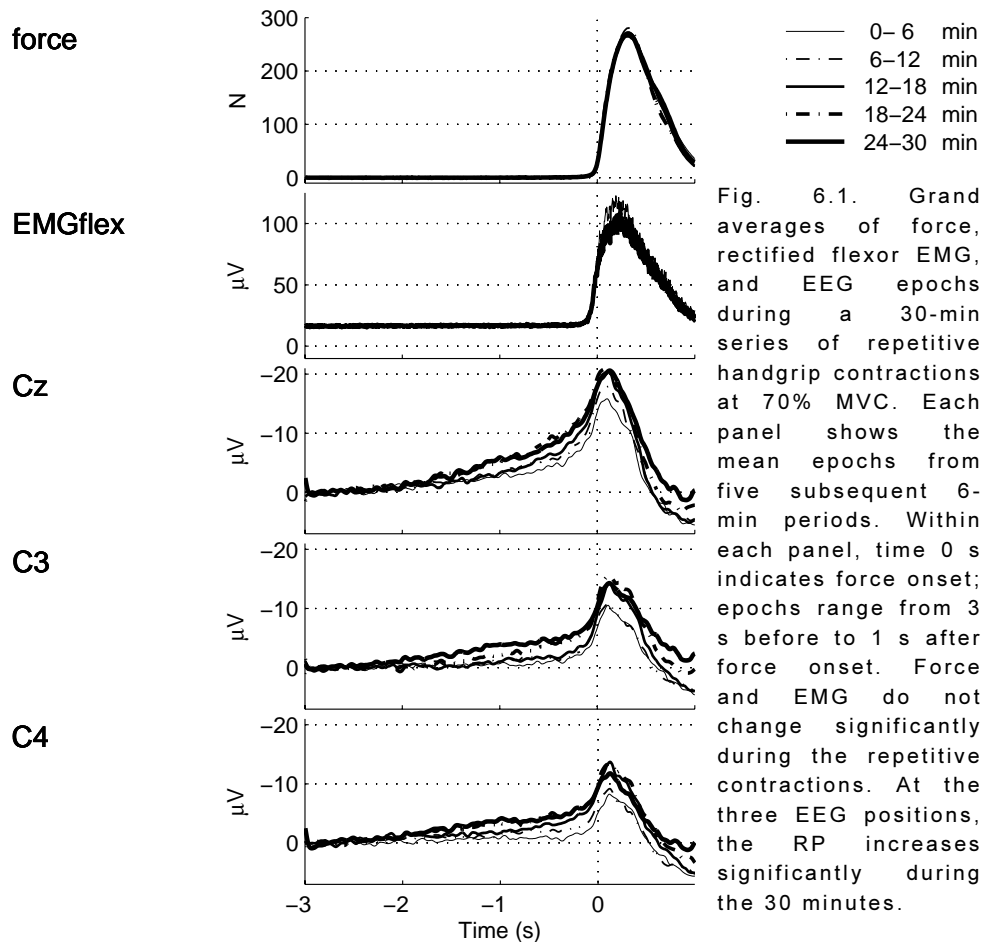


Fig. 6.1. Grand averages of force, rectified flexor EMG, and EEG epochs during a 30-min series of repetitive handgrip contractions at 70% MVC. Each panel shows the mean epochs from five subsequent 6-min periods. Within each panel, time 0 s indicates force onset; epochs range from 3 s before to 1 s after force onset. Force and EMG do not change significantly during the repetitive contractions. At the three EEG positions, the RP increases significantly during the 30 minutes.

1.49 (0.80) s before force onset during the first and 1.86 (0.84) s before force onset during the last 6-min period. At electrodes C3' and C4' initially negativity onset was 1.00 (0.70) and 1.00 (0.82) before force onset; during the last 6-min period this was 1.62 (1.01) s and 1.70 (0.95) s before force onset, respectively.

At Cz, C3' and C4' areas under the curve (2.0 to 0.0 s before force onset) increased significantly during the repetitive contractions (Cz: $t = 2.80$, $p = 0.015$; C3': $t = 2.28$, $p = 0.040$; C4': $t = 4.18$, $p = 0.001$). The area of Cz almost doubled from -6.7 (5.7) to -11.9 (9.2) mV*ms; the areas of C3' and C4' increased fourfold from -1.8 (5.9) to -7.5 (8.1) mV*ms and from -1.7 (6.1) to -7.3 (6.6) mV*ms, respectively.

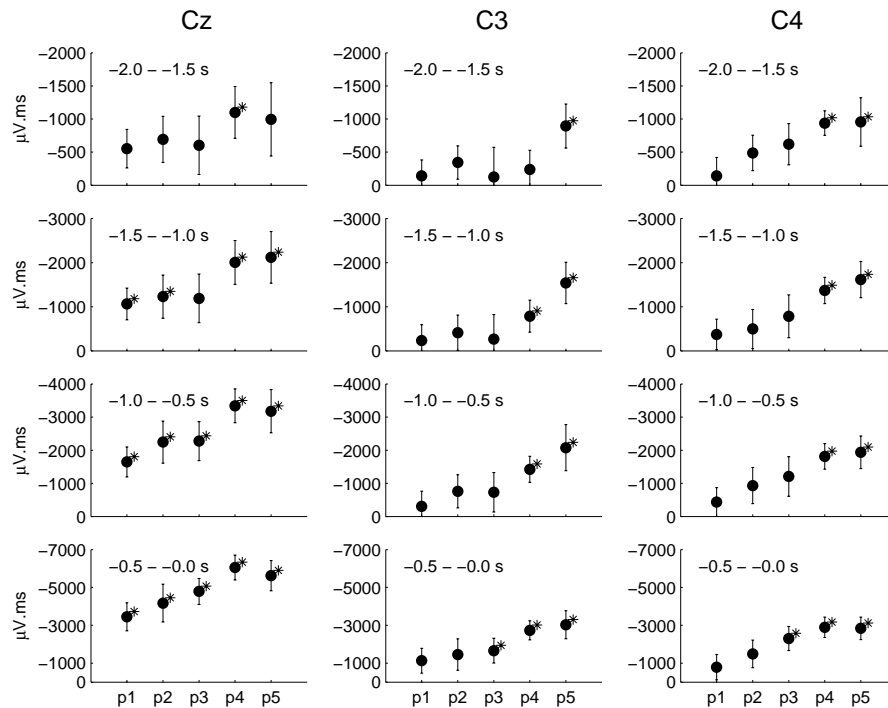


Fig. 6.2. Areas under four intervals of the RP curves during a 30-min series of repetitive handgrip contractions at 70% MVC. The left column shows electrode Cz, the middle column electrode C3', and the right column electrode C4'. Highest panels show the interval longest before force onset, lowest panels show the interval just before force onset. Within each panel, the indications 'p1' ... 'p5' at the x-axis indicate the 5 subsequent 6-min periods (0-6 min, 6-12 min, 12-18 min, 18-24 min, 24-30 min, respectively). Error bars show standard errors of the mean. Asterisks show values significantly deviating from zero. Notice the increase of the areas under the curve during the 30-min series.

Fig. 6.2 shows the areas under the curve for the four intervals of RP (2.0 – 1.5, 1.5 – 1.0, 1.0 – 0.5 and 0.5 – 0.0 s before force onset). Asterisks show areas that deviate significantly from zero. At Cz, the last three interval areas (Fig. 6.2, first row, three most right panels) showed a significant increase over the five 6-min periods ($t = 1.03$, $p = 0.322$; $t = 2.36$, $p = 0.035$; $t = 2.84$, $p = 0.014$ and $t = 2.91$, $p = 0.012$ respectively). At C3', the areas of the first three intervals (Fig. 2, second row, three most left panels) showed a significant increase over the five 6-min periods ($t = 2.16$, $p = 0.050$; $t = 2.48$, $p = 0.028$; $t = 2.16$, $p = 0.050$; $t = 1.95$, $p = 0.074$,

respectively). At C4', the areas of all intervals (Fig. 6.2, third row) increase significantly over the five 6-min periods ($t = 3.32$, $p = 0.006$; $t = 4.61$, $p < 0.001$; $t = 4.07$, $p = 0.001$; $t = 3.24$, $p = 0.006$, respectively).

The relative size of the final MVC did not correlate with the slope of the area under the total curve at any electrode position (Cz: $R = 0.097$, $p = 0.724$; C3': $R = -0.413$, $p = 0.143$; C4': $R = -0.175$, $p = 0.551$), nor with any slope of the areas under the curve of the separate 0.5 s-intervals.

Discussion

This study shows a clear increase of the RP in the presence of only small physiological fatigue during a 30-min series of repetitive handgrip contractions at 70% MVC. During the first 6-min period, a significant negative deviation from baseline was only recognized at electrode Cz starting 1.5 s before force onset. In the course of the 30 minutes, negativity reaches significance also at electrodes C3' and C4' and its start becomes earlier.

Although a slight increase of the RP may be necessary to compensate for small (maximally 8%) peripheral changes^{41,74}, the extent of RP increase suggests that MI and SMA compensate for additional, central, force reducing factors. That peripheral fatigue alone is not enough to explain the increase of the RP is confirmed by the absence of a correlation between the decrease of MVC and the increase of RP, and by the absence of significant changes in the (peripheral) EMG.

The large RP increase in comparison with only little physiological fatigue is in accordance with Freude and Ullsperger's⁴¹ findings during repetitive contractions at 20% MVC. They saw an increase of the RP in the supposed absence of peripheral fatigue, and suggested the influence of required concentration and attention for this low force level task as a possible explanation. However, our results contrast with Freude and Ullsperger's⁴¹ observation that RP was constant during repetitive contractions at 50% MVC.

In our protocol, changes in the central nervous system seem to reduce central efficiency during repetitive contractions. In order to still produce the required force level, motor cortical activity is

increased. It can only be speculated which specific processes hinder force production. Reduction of the level of force output relative to the amount of motor cortex activity may indicate a decreasing efficiency of the motor cortex itself during the repetitive contractions. Besides, activity of other force influencing areas might be involved. A recent PET study that measured regional cerebral blood flow after sustained contractions revealed a gradual increase of activity with the level and duration of muscle contraction in the contralateral MI, primary and secondary somatosensory areas, somatosensory association area, and the temporal areas AA and AI; SMA and cingula activity increased bilaterally⁸⁵. In addition, fMRI showed increasing activity of both the ipsilateral and contralateral primary sensorimotor areas, the SMA, prefrontal cortex, cingulate gyrus and cerebellum during both repetitive and sustained submaximal contractions⁹⁹.

We decided to measure at Cz, C3' and C4', because these positions are situated above the SMA and left and right MI, respectively. The later onset of negativity at C3' and C4' (1.00 s before force onset) in comparison with Cz (1.49 s before force onset) in the first 6-min period is in accordance with the finding that activity of the SMA precedes activity of MI³². The change of onset of negativity in C3' during the 30-min series suggests that activity of the contralateral MI starts to develop earlier to prevent central fatigue. This change in activity was also found at C4'. Bilateral occurrence of the RP is widely recognized³², but this finding suggests that also the ipsilateral cortex increases activity during repetitive contractions. The results of Johnston et al.⁷⁴ showed the same pattern. Indeed, an increase of ipsilateral cortical activity with fatiguing exercise is reported in SMA⁸⁵ and the primary motor cortex⁹⁹. The idea is also supported by data of Zijdwind and Kernell who measured increasing EMG activity in the contralateral homologous muscle during fatiguing contractions¹⁸⁵. However, it is difficult to explain why the negativity at C4' had about the same size as the negativity at C3'. Brunia et al.¹⁹ suggest that subcortical sources cause bilateral activity. Though, we cannot exclude that volume conduction of electric fields originating from the SMA contributes to the signals measured at

C3' and C4'. Techniques to determine which sources are responsible for the changing RP unfortunately need a different experimental design and registrations from more electrode positions¹²⁹.

To conclude, our study shows an increasing RP in the almost absence of physiological fatigue during repetitive contractions at a high force level. The RP seems to represent adaptations to prevent central fatigue in healthy subjects during exercise that induces relatively little peripheral fatigue. The protocol provides an interesting tool to study the decrease of central efficiency and offers prospects for studies in patients with diminished central activation.

Section 3

Physiological fatigue in patients

Chapter 7

Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome

Adapted from:

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Abstract

We have investigated whether central activation failure (CAF) is increased during local muscle fatigue in chronic fatigue syndrome (CFS). Fourteen female CFS patients and 14 age-matched healthy female controls made a 2-min sustained maximal voluntary contraction (MVC) of the biceps brachii muscle. Before, during, and after sustained MVC, electrical endplate stimulation was applied. Force and five-channel surface EMG (sEMG) were registered.

Although force responses upon stimulation during rest did not differ between patients and controls, MVC was significantly lower in patients. Already at the beginning of sustained MVC, CFS patients showed significantly larger CAF than controls ($36.5 \pm 17.0\%$ and $12.9 \pm 13.3\%$ respectively). For all individual patients mean CAF over the first 45 s was higher than 30%, while it was below 30% for all controls. Less peripheral fatigue in patients was demonstrated by the changes in muscle fibre conduction velocity and the differences between force responses before and after contraction.

Central activation is diminished in CFS patients. Possible causes include changed perception, impaired concentration, reduced effort and physiologically defined changes, e.g. in the corticospinal excitability or the concentration of neurotransmitters. As a consequence, demands on the muscle are lower, resulting in less peripheral fatigue. The underlying pathophysiological processes remain still to be determined.

Introduction

Chronic fatigue syndrome (CFS) is defined by severe fatigue of at least 6 months duration that interferes substantially with occupational, educational, social, or personal activities, is not alleviated by rest, and is accompanied by at least four of eight specific symptoms (unrefreshing sleep, sore throat, tender lymph nodes, muscle pain, joint pain, impaired memory or concentration, headache, severe post-exertional fatigue)⁴³. Although much research has been done, physiological processes playing a role in this disease remain uncertain.

Kent-Braun et al.⁸² described that patients suffering from CFS develop relatively large central fatigue during a 4-min sustained maximal contraction of the tibialis anterior muscle. They found a significantly diminished central activation at the end of sustained contraction. Interestingly, they showed that already at the start of exercise in CFS patients force could be added to MVC by superimposed electrical stimulation, indicating that central activation was submaximal. This was not the case in healthy subjects. However, this difference did not reach statistical significance, probably because of the small number (N=7) of both patients and controls. It could also be influenced by the heterogeneity of the groups (both men and women). One might expect lowered central activation to have resulted in decreased peripheral fatigue due to the smaller demands on muscle capacity. However, no significant differences were found, although measures for peripheral fatigue tended to show lower values in CFS.

Other authors, studying short or repetitive contractions and investigating different muscle groups, did not report such a lack of central activation in CFS. Fulcher and White⁴⁴ found no significant difference between CFS patients and controls in the number of subjects that showed a force increase during a short MVC of the quadriceps muscle after additional stimulation. Lloyd et al.¹⁰⁰ made subjects perform repetitive contractions of the elbow flexors at 30% MVC, intermitted by a short MVC with a superimposed electrical stimulus every five minutes. This experiment, also, did not reveal any change in central activation in CFS patients, neither at the start nor at the end of the experiment.

In view of the conflicting results and in order to interpret studies investigating corticospinal excitability in CFS^{17,135,136,161}, we studied central activation in the course of a sustained maximal contraction of the biceps brachii muscle in a larger and more homogeneous (all female) group of CFS patients and healthy controls.

Methods

Patients

Fourteen female CFS patients (mean age 28.6, range 18-37 years), all fulfilling the CDC criteria for CFS⁴³, and 14 age-matched female healthy controls (mean age 26.7, range 21-37 years) were included. None of the subjects reported a history of neuromuscular problems. The protocol was approved by the local ethics committee and all subjects gave written informed consent.

Experimental set-up

The experimental design was used earlier in a study of peripheral and central aspects of fatigue during a sustained maximal voluntary contraction in healthy subjects¹⁴⁰. It was based on the twitch interpolation technique. This and similar methods to determine central activation failure (CAF), were used earlier in several studies on healthy subjects and patients with for example CFS, fibromyalgia, stroke, multiple sclerosis, and post-polio⁴⁸. The reliability of measures of maximal voluntary activation determined with twitch interpolation for elbow flexor muscles has been described by Allen et al.⁴.

Subjects sat in a chair with their left arm fixed in a dynamometer in a horizontal position with the shoulder in abduction, the elbow in a right angle and the forearm supinated. Trunk and elbow were stabilised using custom made pads. The force of elbow flexion was measured at the wrist. Force was sampled at a rate of 2 kHz and lowpass filtered (1 kHz). The maximal resolution of force measurement was 0.1 N bit⁻¹.

SurfaceEMG (sEMG) was measured using a multi-electrode array of five gold-coated electrodes that were placed in line (electrode diameter 2 mm; inter electrode distance 3 mm) parallel to the fibre

direction of the biceps brachii muscle, distal to the motor points. A reference electrode was placed at the elbow joint. During placement of the electrode array, both monopolar and bipolar EMG was monitored visually. Values of impedances and cross correlations between the adjacent electrode positions were checked. If electrode placement was not satisfactory, the device was replaced. The available space to vary the position of the electrode array was limited because the array was placed distally from the surface electrodes used for electrical stimulation. Especially in women with shorter arms or arms with a relatively thick fat layer, placement was difficult. The position that was chosen could not be changed during the sustained contraction. Possibly, small lateral displacement of the muscle tissue slightly altered the electrode position during 100% MVC.

Monopolar signals were amplified, bandpass filtered (3.2-800 Hz) and A/D-converted (16 bits with a resolution of 0.5 mV bit^{-1} at a rate of 4 kHz/channel).

A custom-made time code generator synchronised force- and sEMG-data.

Using surface electrodes, electrical endplate stimulation was applied over the motor points of the medial and lateral head of the biceps brachii muscle. As the basic 'unit of stimulation' a 40 ms stimulus train of 5 rectangular pulses (each with a duration of 100 μs) with a 10 ms interval (100 Hz) was used. Five stimulus trains were combined to form a stimulus event (SE)¹⁴⁰. Based on a pilot study, the inter train interval was 300 ms during voluntary contraction. This provided intervals long enough to avoid interference of subsequent force responses, but kept the duration of the SEs as short as possible. During rest this interval was 1000 ms, while these force responses have a longer duration. The five subsequent force responses to a SE were averaged and this average will be referred to as the force response. A pilot study, which was designed to test the utility of this stimulus pattern in CAF determination, showed a strong correlation between the instructed submaximal voluntary force level and the amplitude of the force response.

Before the experiment, for every subject stimulus optimisation was performed by slowly increasing the intensity until no further

increase of force response resulted from the increase of intensity or –in 3 CFS patients and 1 control subject– until pain limited further increase. All SEs were given at this intensity level (CFS: range 26.0-53.5, mean 38.2 mA, controls: range 26.0-53.4, mean 40.8 mA).

Protocol

Before any exercise, the subject made three short MVCs of the biceps brachii muscle with a 1-min interval. After a 10-min rest, an initial SE was applied while the subject's biceps brachii muscle was relaxed, resulting in the initial force response. Next, the subject performed a 2-min sustained MVC of the biceps brachii muscle. SEs were given every 15 s, leading to superimposed force responses. Verbal encouragement was given throughout and force was visually fed back to the subject. Immediately after the sustained contraction, a final SE was applied while the muscle was relaxed, resulting in the final force response.

Force analysis

All voluntary force values shown are mean values over 2 s of data just before stimulation, except for the value of MVC before the sustained contraction, which is the true maximum.

Force responses upon stimulation during sustained MVC were corrected for changes of voluntary force via linear interpolation between the moment of stimulation and 300 ms after. Then, a correction was made for the influence of peripheral fatigue on the size of the superimposed force responses during MVC, as described in Schillings et al.¹⁴⁰. So, CAF was defined as:

$$\text{CAF}^t = F_{sx}^t / (F_s^b - t/120 * (F_s^b - F_s^e)) * 100\%$$

where F_{sx}^t is the amplitude of the superimposed force response during MVC, F_s^b and F_s^e are the initial and final force responses respectively while the arm was relaxed, and t is time in seconds.

SEMG analysis

SEMG values used were calculated from 2 s of data just before stimulation. Muscle fibre conduction velocity (MFCV)^{108,188} was determined from four out of five electrodes. The upper limit of MFCV was set at 8 m s⁻¹, based on physiological limits¹⁴⁰. As a

result, two CFS patients and five healthy controls were excluded from MFCV analysis since their MFCVs exceeded this value at least three times. Besides, only two data points showed non-physiological values. The influence of far-field potentials, alignment of electrodes and fibre direction and placement of electrodes in relation to the end plate position might have contributed to the non-physiological values. MFCV determination has a tendency for higher values with only small inaccuracies of electrode placement¹⁸⁸, but these deviancies are likely to be consistent if electrodes are not replaced. Therefore, only relative MFCV values were used in further analysis. Thus, MFCV was expressed as a percentage of MFCV right at the start of sustained MVC^{105,140}. MFCV values were not involved in the calculation of other values. Root mean square (RMS) values presented are means of the RMS values of the electrodes also involved in MFCV determination.

Statistics

Normality was tested according to the Kolmogorov-Smirnov test. For each subject, linear regression analysis, performed on the nine data points via the least squares method, determined the slopes of CAF, MFCV and MVC during the 2-min sustained contraction. T-values were used to test if slopes deviated from 0. Between-group differences were analysed with independent samples t-tests. Differences between initial and final force responses were tested using paired samples t-tests. Significance level was set at $p = 0.05$ (two-tailed).

Results

All variables showed a normal distribution. Presented values are means (standard deviations).

Force responses to stimulation before voluntary contraction had a mean amplitude of 11.6 (4.6) N in CFS, which did not differ from 11.3 (3.0) N in healthy subjects ($p = 0.827$). MVC before exercise was 114.0 (27.7) N in patients, which was significantly smaller than 178.2 (41.1) N in controls ($p < 0.001$).

Directly at the beginning of sustained MVC, mean voluntary force over 2 s in CFS was 86.7 (23.4) N, while healthy controls reached

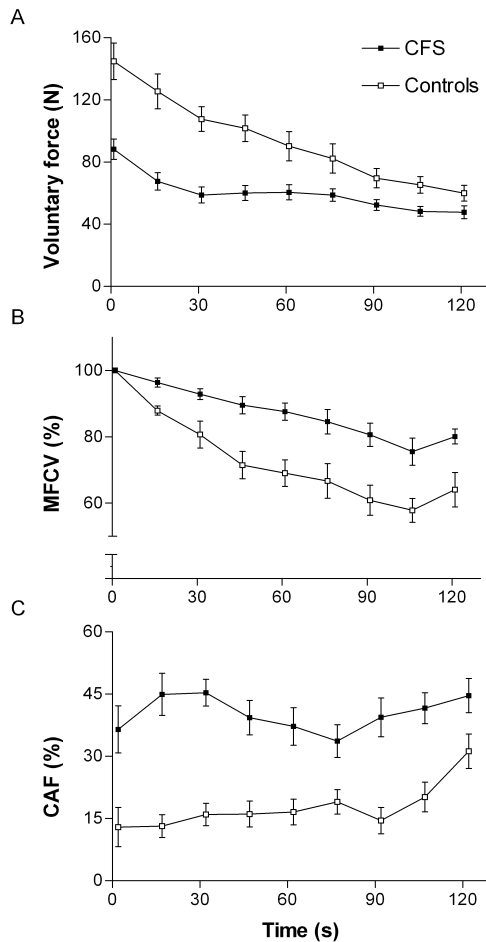


Fig. 7.1. Voluntary force (A), muscle fibre conduction velocity (B), and central activation failure (C) during a 2-min sustained maximal voluntary contraction. Mean and SEM values are presented. Healthy controls produce higher voluntary force than patients (CFS: $N = 14$; controls: $N = 14$). Muscle fibre conduction velocity (MFCV) changes less in patients than in healthy controls, indicating smaller demands on muscle capacity in patients (CFS: $N = 10$; controls: $N = 9$). Central activation failure is higher in patients over the whole period (CFS: $N = 14$; controls: $N = 14$).

a significantly higher value of 144.9 (43.8 N) ($p < 0.001$) (Fig. 7.1A). This difference in voluntary force was also expressed in sEMG amplitudes: in CFS subjects RMS showed a mean value of 0.9 (0.4) mV at the beginning of sustained MVC, which was 1.6 (0.8) mV in healthy controls ($p = 0.011$).

All subjects succeeded in maintaining MVC for 2 minutes. As is shown in Fig. 7.1A, in both groups voluntary force decreased during the sustained contraction (CFS: slope = $-0.25 (0.14) \text{ N s}^{-1}$, $p < 0.001$; controls: slope = $-0.69 (0.22) \text{ N s}^{-1}$, $p < 0.001$). The slope in the control group was significantly steeper than in CFS ($p < 0.001$). The absolute voluntary force did not significantly differ

between both groups at the end of sustained contraction (CFS: 47.6 (14.2) N, controls: 59.9 (18.8) N).

A force decrease, although smaller, was found also when comparing initial and final force responses to electrical stimulation. In CFS patients, the final force response – to stimulation of the relaxed muscle after sustained contraction – was 76.9 (18.1)% of the initial force response – to stimulation of the relaxed muscle before sustained contraction. In healthy controls, who did their sustained MVC at a higher absolute force level, this relative final force response was significantly lower (45.9 (12.5)%, $p < 0.001$).

The initial absolute MFCV value did not differ between both groups (4.9 (0.9) ms^{-1} for CFS and 4.7 (1.2) ms^{-1} for controls). MFCV decreased significantly during the sustained contraction (CFS: slope = -0.20 (0.10)% s^{-1} , $p < 0.001$; controls: slope = -0.39 (0.15)% s^{-1} , $p < 0.001$, Fig. 7.1B), although patients showed a smaller relative MFCV slope than controls ($p = 0.004$).

Also CAF differed between both groups (Fig. 7.1C). Already immediately after the start of exercise, CAF was higher in patients than in controls (CFS: 36.5 (17.0)%, controls: 12.9 (13.3)%; $p = 0.005$). CAF values averaged for each subject from the first 45 s of sustained contraction provide a full separation between both groups: all patients showed averaged CAF values above 30%, while all controls had values lower than 30% (Fig. 7.2). CAF changed significantly with time in controls (slope = 0.11 (0.10)% s^{-1} , $p < 0.01$), but not in CFS patients (slope = 0.005 (0.080)% s^{-1}). Controls at the end of exercise showed CAF values similar to those of patients at the start of exercise.

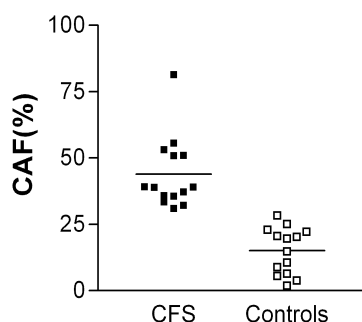


Fig. 7.2. Averaged central activation failure from the first 45 s of sustained contraction in all individual subjects. Notice that all CFS patients show values higher than 30%, while all healthy controls show values below 30%. Horizontal lines show mean values (CFS: $N = 14$; controls: $N = 14$).

Discussion

The results of this study show that central activation is strongly diminished in CFS during sustained MVC of the biceps brachii muscle. While force responses upon electrical stimulation before exercise indicate that the initial muscle capacity does not differ between healthy controls and CFS patients, MVC is lower in patients both before exercise and directly at the start of sustained MVC. From the relatively large force responses added by electrical stimulation during MVC, we conclude that this voluntary force difference results from the larger CAF in CFS patients. During sustained MVC, controls show an increase of CAF, but it remains at a higher level in patients during the full 2-min sustained contraction.

The occurrence of reduced central activation is confirmed by the indicators of peripheral fatigue: both the decrease of MFCV during exercise¹⁸⁸ and the ratio between the force responses before and after exercise^{100,163} show that the demands on the muscle have been sub-maximal in patients. It is important to notice that these latter differences do not suggest that peripheral functioning differs between both groups.

Our results are in accordance with those of Kent-Braun et al.⁸² who found that central activation of the tibialis anterior muscle was diminished in CFS during sustained MVC. They did not show significant differences in peripheral muscle functioning between patients and controls, but peripheral measures showed a tendency to lower demands on muscle capacity in the patient group. In contrast, our findings seem to be in contradiction with Gibson et al.⁵⁶ and Lloyd et al.¹⁰⁰, who did not detect CAF during short MVC of the quadriceps and the elbow flexor muscles respectively.

The magnitude of CAF at the start of sustained MVC in CFS is similar to that in hemiparetic quadriceps of stroke patients¹¹⁶ and not different from that in the ankle dorsiflexors of ALS patients⁸¹. In contrast, central activation of the adductor pollicis in multiple sclerosis is almost maximal at the start¹⁵². It declines during sustained MVC¹⁵², as it does in ALS⁸¹. In quadriceps of patients with fibromyalgia, a disorder with symptoms similar to those of CFS, enlarged CAF before fatigue has been described^{118,119}. Elbow

flexors of these patients, however, did not show abnormal central activation¹¹¹.

Except for the paper of Fulcher and White⁴⁴ who measured quadriceps strength, we have found no literature describing differences in voluntary force between controls and CFS patients, although several studies assessing various muscle groups have been done^{56,82,100,101,134-136,163}. However, the majority of studies on CFS did show - although not significantly - lower MVC values in patients, as can be seen in Table 7.1. In seven out of nine studies, MVC in patients was between 6.8 and 33.9% lower than in controls. We hypothesise that the absence of statistical significance in many studies originated in the heterogeneity of the population studied. The earlier studies could not use the rather strict CDC criteria that we used⁴³, which might have led to contamination of the CFS group with other patients. Besides, except for Lloyd et al.^{100,101} who separately presented male and female data, these studies showed values of men and women intermingled. Both factors may have increased the variability of MVCs and therefore hindered the identification of significant force differences. Thus, we conclude that the present MVC data are not really contradictory with earlier results. In fact it did show significant differences, because we studied a more homogeneous group of patients.

Author	Muscle group	Controls		CFS		MVC		Rel. diff. (%)	sign.
		N♂	N♀	N♂	N♀	controls	CFS		
Lloyd et al. ¹⁰¹	Elbow flexors	10		10		66 Nm	75 Nm	13.6	ns
			10		10	44 Nm	41 Nm	-6.8	ns
Lloyd et al. ¹⁰⁰	Elbow flexors	13	0	12	0	68 Nm	69 Nm	1.6	ns
Rutherford & White ¹³⁴	Quadriceps	6	5	4	7	514 N	448 N	-12.8	ns
Gibson et al. ⁵⁶	Quadriceps	6	6	6	6	476 N	443 N	-6.9	ns
Kent-Braun et al. ⁸²	Tibialis anterior	6	1	4	3	62 N	41 N	-33.9	ns
	Extensor carpi								
Samii et al. ¹³⁶	radialis	?N=18?		?N=12?		12 N	10 N	-10.3	ns
Sacco et al. ¹³⁵	Elbow flexors	4	6	4	6	181 N	160 N	-11.6	ns
Fulcher & White ⁴⁴	Quadriceps	8	22	17	49	442 N	310 N	-29.9	0.001

Table 7.1. Literature comparing maximal voluntary force between CFS patients and healthy controls. The column 'relative difference' is computed by dividing the MVC difference by the MVC value of the controls. The last column shows if differences are significant.

What can be the cause of the decline of central activation in CFS? The answer can be sought at several levels of the nervous system. Vecchiet et al.¹⁷⁸ reported that CFS patients have enhanced pain perception upon electrical stimulation in their muscle tissue. This could mean that patients compared to controls experience more pain relative to the amount of peripheral impairment, which could lead to negative feedback and thus inhibition of muscle activation. Besides, several studies^{44,55,56,101,135} report higher perceived effort during exercise, which may induce a reduction of the performance. Fear of physical movement and activity in CFS patients has the same effect¹⁵⁷. Thus, changed perceptions may down-regulate central activation in our maximal sustained force task.

Impaired concentration or decreased motivation may also contribute to CAF^{4,82}. Because experienced concentration problems belong to the key symptoms of CFS⁴³, concentration appears likely to be playing an important role in our findings. However, because of the inconsistency between results of different studies^{57,130,139}, it seems to be task-dependent whether patients focus their attention as well as healthy subjects. Therefore, it is unsure if concentration problems may be responsible for enlarged CAF in our protocol.

The role of motivational problems in CFS is still controversial, although some authors have argued that motivation does not seem to be changed⁵⁷. In our protocol, we tried to keep motivation as strong as possible in both subject groups by active verbal encouragement. In a task originally designed to detect malingering, Van der Werf et al.¹⁷⁴ showed that 30% of the CFS patients obtained scores indicative of reduced effort. Because the present study showed increased CAF in 100% rather than in about 30% of the patients, we propose that reduced effort will at least not totally account for the diminished central activation.

Beside these psychological factors, more physiologically defined changes in the central nervous system can be proposed as contributors to diminished central activation. Changed corticospinal excitability may be present^{17,135,136,161}, possibly caused by altered facilitating or inhibitory processes in for instance motor or premotor areas. Changed concentrations of neurotransmitters in

CFS⁵⁵ may play a role in this. To what extent these physiological processes reflect the psychological ones or vice versa is unclear.

It is important to be aware of the influence of reduced central activation during MVC determination on studies requiring exercise at a certain relative force level. From the above, we must conclude that in studies comparing healthy and CFS subjects, patients probably often did their task at a lower absolute force level, so that smaller demands on muscle capacity were made. This might for example explain the observation of differences in cortical activation levels as found by Samii et al.¹³⁶ and Sacco et al.¹³⁵. However, Samii et al.¹³⁷ show that postexercise facilitation, which is measured in their paper on CFS¹³⁶, is hardly influenced by the force level at which a contraction is made in healthy subjects. Though, in the discussion of studies on CFS the influence of a lower absolute force level should considerably be taken into account.

Our data showed that all individual CFS patients, diagnosed according to the CDC criteria⁴³, could have been identified only based on their CAF value at the start of sustained contraction (>30%). Therefore, our study does not only serve a theoretical understanding of the disease, but also provides an additional practical method that could support diagnosis.

Chapter 8

Experienced and physiological fatigue in neuromuscular disorders

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Submitted

Abstract

Fatigue has been described as a typical symptom of various neurological diseases. It might be caused both by changes at the peripheral and at the central level. This study measured the level of experienced fatigue and physiological correlates of local muscle fatigue in three genetically defined neuromuscular disorders.

65 Facioscapulohumeral dystrophy (FSHD), 79 classical myotonic dystrophy (MD), 73 hereditary motor and sensory neuropathy type I (HMSN) patients and 24 age-matched healthy controls made a 2-min sustained maximal voluntary contraction of the biceps brachii muscle. Experienced fatigue at the current moment was assessed with the abbreviated fatigue questionnaire just before the physiological measurement. Peripheral fatigue was quantified by comparing the amplitudes of an initial and a final stimulated force response during rest. Muscle fibre conduction velocity was determined from a 5-channel surface EMG recording in order to show peripheral changes during the contraction. Central aspects of fatigue were measured using superimposed electrical endplate stimulation. Two weeks later, the Checklist Individual Strength subscale fatigue (CIS-fatigue) was used to determine the level of experienced fatigue of the past two weeks.

More than 50% of the neuromuscular patients showed severe experienced fatigue. Total physiological and peripheral fatigue was smaller in patients compared to controls, and central fatigue was normal. The most interesting result of this study was the presence of a large central activation failure (CAF) in all groups of neuromuscular patients; they showed CAF values of 36 - 41% already at the start of sustained contraction, whereas the control group showed only 12%. CAF correlated with the level of experienced fatigue just before the test.

The cause of the large CAF in patients is unclear. Reduced concentration, motivation or effort can lead to lower central activation. In neuromuscular patients especially fear of physical activity or fear to damage the muscle or nerve tissue may contribute. Besides, also physiological feedback mechanisms or changes at the motocortical level may be a cause of reduced central activation.

Introduction

Fatigue is a typical symptom of various neurological diseases²⁴. It is present in more than 60% of patients with a neuromuscular disorder^{75,107,124}. In Parkinson's disease, more fatigue is associated with less physical activity, worse physical function, and lower functional capacity⁵². In current literature, the term fatigue indicates both experienced fatigue and types of physiological fatigue.

Experienced fatigue has been defined as a difficulty in initiation of or sustaining voluntary activities²⁴. Krupp and Polina⁸⁹ have described it to be an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion. The symptom is distinguished from weakness⁸⁹ and does not necessarily correlate with signs of physiological fatigue⁷². This latter point, however, is not always properly recognised in literature.

Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force⁴⁸. It is divided into peripheral and central components, a division based on whether a loss of capacity to generate a maximum force originates in the muscle tissue or in the nervous system, respectively. During a sustained maximal voluntary contraction (MVC), healthy subjects develop both peripheral and central fatigue^{78,140}. The occurrence of central fatigue means that central activation worsens during the contraction. Central activation, however, is sub-optimal already at the start of a sustained MVC¹⁴⁰.

Literature about physiological fatigability in neuromuscular patients is scarce. It is an interesting phenomenon, because the muscle itself - the motor of movement and force - is affected. McComas and co-workers¹⁰⁶ have described that increased fatigability inevitably occurs in patients with muscle weakness, regardless whether the latter is due to a central or a peripheral neurological disorder. Not only (possibly indirect) peripheral changes, but also central changes could be responsible for this. Recently, alterations in the central nervous system have been described in neuromuscular disorders^{26,34,45,95,112,121,156}, but their influence on fatigue has not yet been studied.

The aim of the present study was to investigate both peripheral and central aspects of physiological fatigue during a sustained MVC in neuromuscular patients. We correlate these factors of physiological fatigue to the level of experienced fatigue just before the test. To get a broad overview of different types of neuromuscular disorders and to find possible disease specific mechanisms playing a role in the development of fatigue, we studied three genetically characterised neuromuscular disorders: facioscapulohumeral muscular dystrophy (FSHD), a myogenic disorder; hereditary motor and sensory neuropathy type Ia (HMSN), a neurogenic disorder; and myotonic dystrophy (MD), a multisystem disorder.

Subjects and methods

Subjects

Age-matched groups of 65 FSHD-, 79 classical MD-, 73 HMSN-patients and 24 neurologically healthy controls participated in the study (Table 8.1). Patients registered in our hospital or at the Dutch Neuromuscular Diseases Association (Vereniging Spierziekten Nederland, VSN) were recruited. Only ambulant patients, age 18-60 years, able of passive abduction of the left shoulder to 90° were included.

Disease severity was determined with the Medical Research Council grading scale (MRC; 0 to 5) investigating the strength of the shoulder abductors, grip force, foot extensors and knee extensors. In order to characterise the patients, these eight values (both left and right) were averaged (Table 8.1). In healthy subjects the mean MRC was 5.0 by definition. In order to verify the diagnoses, the patients' neurologists were contacted. In part of the patients, the diagnosis was genetically confirmed (Table 8.1).

The protocol was approved by the Committee on Research Involving Human Subjects Region Arnhem-Nijmegen. All subjects gave their written informed consent before participation.

Experienced fatigue

Just before the start of the physiological protocol, all patients and 16 controls filled out the 4-item abbreviated fatigue questionnaire

(AFQ)² referring to the level of experienced fatigue at the current moment. Scores range from 4 to 28; higher scores indicate higher levels of fatigue. Fourteen days later, patients filled out the Checklist Individual Strength subscale fatigue (CIS-fatigue) evaluating the level of experienced fatigue during the past two weeks¹⁸². Scores of this 8-item questionnaire range from 8 to 56. Values ≥ 35 indicate severe fatigue¹⁴⁶. Controls only answered the AFQ.

	total	N		mean	Age		Mean MRC			DNA conf.
		♂ (%)	♀ (%)		SD	range	mean	SD	range	
FSHD	65	58.5	41.5	43.1	10.3	22.5-60.9	3.6	0.8	1.9-5.0	83.1%
MD	79	55.7	44.3	41.0	9.8	22.5-56.6	3.7	0.8	2.0-5.0	62.0%
HMSN	73	41.1	58.9	42.4	9.8	20.0-58.0	3.7	0.9	1.5-5.0	45.2%
control	24	50.0	50.0	42.1	13.5	21.7-59.3	5.0	0.0	5.0-5.0	

Table 8.1 Details of subject groups

Physiological factors of fatigue

Experimental set-up

The experimental design has been used earlier in studies into peripheral and central aspects of fatigue in healthy subjects¹⁴⁰ and in patients with chronic fatigue syndrome¹⁴¹. It is based on the twitch interpolation technique¹¹⁰.

Subjects sat in a chair with their left arm fixed in a dynamometer in a horizontal position with the shoulder in abduction, the elbow in a right angle and the forearm supinated. Trunk and elbow were stabilised using custom made pads. The force of elbow flexion was measured at the wrist. Force was sampled at a rate of 2 kHz and low-pass filtered (1 kHz). The maximal resolution of force measurement was 0.1 N bit⁻¹.

Surface EMG (sEMG) was measured using a multi-electrode array of five gold-coated serrated electrodes¹⁵ that were placed in line (electrode diameter 2 mm; inter electrode distance 3 mm) parallel to the fibre direction of the biceps brachii muscle, distal to the motor points. A reference electrode was placed at the elbow joint. Monopolar signals were amplified using a 64-channel amplifier system (MARK 6, Biosemi, Amsterdam, The Netherlands), band-pass filtered (3.2-800 Hz) and A/D-converted (16 bits with a resolution of 0.5 mV bit⁻¹ at a rate of 4 kHz/channel). A custom-made time code generator synchronised force- and sEMG-data.

Using self-adhesive surface electrodes (Teca NCS2000 disposable surface electrode system) and a general-purpose electrical bio-stimulator (designed and manufactured by the local Department of Technical Engineering), electrical endplate stimulation was applied over the motor points of the medial and lateral head of the biceps brachii muscle¹⁴⁰. A stimulus event consisted of five times a 5-pulse 100-Hz train (duration 40ms). Pulse duration usually was 100 μ s. In 6 FSHD, 6 MD, 32 HMSN, and 1 control subject duration was set at 200 μ s, because force responses to shorter stimulation were very low. The average of the five responses to these short trains is referred to as 'the force response' and is used for analysis. During voluntary contraction the inter-train interval was 300ms, during rest the inter-train interval was 1000ms. Pilot experiments had shown that these inter-train intervals were appropriate to avoid fusion of the single force responses.

Stimulus intensity was determined by increasing the current until the force did not rise anymore or until pain limited further increase. All SEs were given at this intensity level (FSHD: intensity mean 41.5, SD 10.5, range 20.0-72.9 mA; force mean 9.4, SD 4.6, range 1.9-18.4 N; MD: intensity mean 37.4, SD 11.0, range 19.9-88.4 mA; force mean 9.4, SD 5.0, range 1.4-25.9 N; HMSN: intensity mean 46.9, SD 9.7, range 26.0-65.7; force mean 7.2, SD 4.3, range 1.3-21.7 N; controls: intensity mean 44.0, SD 12.2, range 21.0-70.0; force mean 15.7, SD 6.5, range 8.2-31.3 N). The initial stimulus event was not preceded by a short voluntary contraction, because pilot experiments showed that potentiation did not occur with this type of stimulus event.

Protocol

The electrophysiological protocol has been described and visualised earlier^{140,141}. First, subjects made three short MVCs of the biceps brachii muscle with a 1-min interval. After a 10-min rest, an initial SE was applied while the subject's biceps brachii muscle was relaxed, resulting in the initial force response. Then, the subject performed a 2-min sustained MVC of the biceps brachii muscle. SEs were given every 15 s, leading to superimposed force responses. Verbal encouragement was given throughout and real-

time visual feedback of the force was provided. Immediately after the sustained contraction, a final SE was applied while the muscle was relaxed, resulting in the final force response.

Force analysis

Voluntary force values are mean values over 2 s of data just before stimulation, except for the value of MVC before the sustained contraction (MVC^i), which is the true maximum. Values were obtained via Matlab 6.5 (The Mathworks Inc., USA).

Physiological fatigue indicated the total amount of voluntary force lost during the sustained MVC:

physiological fatigue = $(1 - F^{120}/F^0) * 100\%$, in which F^{120} is the voluntary force at the end and F^0 at the start of sustained MVC. A higher score indicates more fatigue.

Peripheral fatigue was determined by:

peripheral fatigue = $(1 - F_s^e/F_s^b) * 100\%$, where F_s^b is the amplitude of the initial (before sustained MVC) and F_s^e the amplitude of the final (after sustained MVC) force response during rest. A higher score indicates a higher loss of force due to peripheral changes, and thus more peripheral fatigue.

Central activation failure (CAF) after t s of sustained MVC was calculated by:

$CAF^t = F_{sx}^t / (F_s^b - t/120 * (F_s^b - F_s^e)) * 100\%$, where F_{sx}^t is the amplitude of the superimposed force response after t s from the start of sustained MVC. In calculating CAF^t , the influence of changing peripheral fatigue on the size of the superimposed force responses during MVC is taken into account, as described earlier¹⁴⁰. CAF was determined using Excel 2000 (Microsoft). A higher value of CAF indicates less central activation.

Central fatigue is defined as the change of CAF during the sustained MVC, thus:

central fatigue = $CAF^{120} - CAF^0$.

A higher score means that more fatigue occurs due to changes at the central level.

SEMG analysis

SEMG values used were calculated with Matlab 6.5 (The Mathworks) from 2 s of data just before stimulation. As described

in more detail before^{140,141}, muscle fibre conduction velocity (MFCV) was determined from four out of five electrodes. The upper limit of MFCV was set at 8 m s⁻¹, based on physiological limits. MFCV is known to decrease with peripheral fatigue^{109,186} and therefore used as a measure of peripheral fatigue during sustained MVC.

Statistical analysis

Differences between controls and the total group of patients were tested with an independent samples t-test. Possible differences between the three patient groups were analysed with one-way ANOVA (analysis of variance). The possible change of a variable during the sustained contraction was determined by linear regression. Slopes as well as the amount of peripheral fatigue were tested by one-sample t-tests.

In correlations in which MRC values were involved, Spearman's ρ was used. These were not calculated for healthy controls, because mean MRC is 5.0 in any control by definition. In other correlations, we used Pearson's coefficient (r). All statistical tests were performed with the Statistical Package for the Social Sciences (SPSS 12.0.1). Significance level was set at $p < 0.05$ (two-tailed).

All values presented are means (standard deviations).

Results

Three subjects (2 HMSN and 1 MD) did not sustain the 2-min MVC. Measurements of two FSHD subjects were stopped because the subjects fainted during detection of the motor points. Measurements of 1 FSHD and 1 MD patient failed because of technical problems. Of these seven subjects no force data was analysed. Electrical stimulation did not result in a sufficient force response in 4 FSHD, 6 MD and 17 HMSN patients. Although no stimulation data was available, other data of this group was used in further analyses.

Experienced fatigue

Answering the AFQ, patients reported a significantly higher level of current experienced fatigue than controls [Table 8.2, Fig. 8.1, AFQ:

$t = 8.4$; $p < 0.001$]. There were no significant differences between the three patient groups. CIS-fatigue revealed high mean scores in patients for the level of experienced fatigue during the past two weeks [FSHD: 32.1 (11.7); MD: 34.1 (10.5); HMSN: 34.9 (12.9)]. More than half of the patients showed CIS-fatigue ≥ 35 , which is considered severely fatigued¹⁴⁶ [FSHD: 50.8%; MD: 53.2%; HMSN: 54.8%]. In all patient groups, AFQ values concerning the current fatigue level correlated significantly with the level of experienced fatigue during the past two weeks (CIS-fatigue) [FSHD: $r = 0.68$, $p < 0.001$; MD: $r = 0.53$, $p < 0.001$; HMSN: $r = 0.78$, $p < 0.001$].

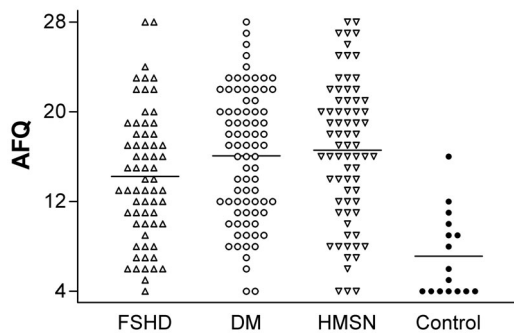


Fig. 8.1. Level of experienced fatigue at the current moment measured with the AFQ just before the physiological protocol. Scores can range from 4 to 28. Higher scores indicate higher levels of experienced fatigue. Each symbol represents an individual subject. Horizontal lines show group averages. Patient groups clearly show higher mean values than the control group, although individual patients might have normal values.

Physiological fatigue

MVC of the biceps brachii muscle before sustained contraction (MVC^i) was significantly [$t = -4.8$; $p < 0.001$] lower in patients than in controls (Table 8.2). ANOVA showed no difference between the three patient groups. MVC at the start of sustained contraction (MVC^0) differed in the same way between the groups [$t = -5.9$; $p < 0.001$] (Fig. 8.2A). MVC^0 correlated negatively with AFQ scores in FSHD and HMSN [FSHD: $r = -0.29$, $p = 0.031$; HMSN: $r = -0.28$, $p = 0.024$].

In all groups, MVC declined significantly during the sustained contraction (FSHD: slope = -0.24 (0.39)% s^{-1} , $t = -4.7$, $p < 0.001$; MD: slope = -0.27 (0.27) s^{-1} , $t = -8.9$, $p < 0.001$; HMSN: slope = -0.26 (0.23)% s^{-1} , $t = -8.9$, $p < 0.001$; controls: slope = -0.44 (0.12)% s^{-1} , $t = -18.2$, $p < 0.001$). This decline was slower in

	MVC ⁱ (N)	Experienced fatigue (AFQ)	Physiological fatigue (%)	Peripheral fatigue (%)	Central fatigue (%)	CAF ^o (%)
FSHD	133.5 (66.0)	14.2 (5.7)	29.3 (48.1)	27.4 (24.0)	4.5(26.6)	33.9 (23.7)
MD	130.6 (64.9)	16.1 (5.8)	37.3 (33.4)	29.5 (26.1)	1.7 (26.6)	41.4 (25.7)
HMSN	148.3 (79.0)	16.6 (6.3)	36.3 (32.6)	34.2 (24.8)	15.1(46.0)	36.4 (23.4)
control	209.8(64.5)	7.1 (3.7)	54.3 (10.9)	50.8 (13.7)	3.9 (13.4)	12.4 (10.7)

Table 8.2 Force and fatigue values

patients than in controls [$t = 3.0$; $p = 0.003$], but did not differ between the patient groups (Fig. 8.2A).

Physiological fatigue, which is the size of the decline of voluntary force, was significantly larger in controls than in patients [$t = -5.6$; $p < 0.001$] and did not differ between the three patient groups. It correlated positively with mean MRC in all patient groups [FSHD: $\rho = 0.34$, $p = 0.010$; MD: $\rho = 0.24$, $p = 0.035$; HMSN: $\rho = 0.45$, $p < 0.001$], and with AFQ in the HMSN group only [HMSN: $r = -0.25$, $p = 0.043$].

Peripheral fatigue

In all groups, the relative amplitude of the final force response - compared with the amplitude of the initial force response - showed that peripheral fatigue had occurred [FSHD: $t = 8.7$, $p < 0.001$; MD: $t = 9.7$, $p < 0.001$; HMSN: $t = 10.3$, $p < 0.001$, controls: $t = 18.2$, $p < 0.001$] (Table 8.2). Less peripheral fatigue occurred in patients than in controls [$t = -6.2$; $p < 0.001$], whereas the three patient groups did not differ.

The course of peripheral fatigue development during the sustained MVC, represented by MFCV values, is shown in Fig. 8.2B. All groups showed a negative slope not different between the groups (FSHD: slope = -0.013 (0.013) m s^{-2} , $t = -6.1$, $p < 0.001$; MD: slope = -0.010 (0.008) m s^{-2} , $t = -9.7$, $p < 0.001$; HMSN: slope = -0.011 (0.009) m s^{-2} , $t = -9.4$, $p < 0.001$; controls: slope = -0.012 (0.008) m s^{-2} , $t = -7.1$, $p < 0.001$).

Peripheral fatigue correlated positively with mean MRC in FSHD [FSHD: $\rho = 0.27$, $p = 0.041$]. It did not correlate with AFQ, neither in patients nor in controls.

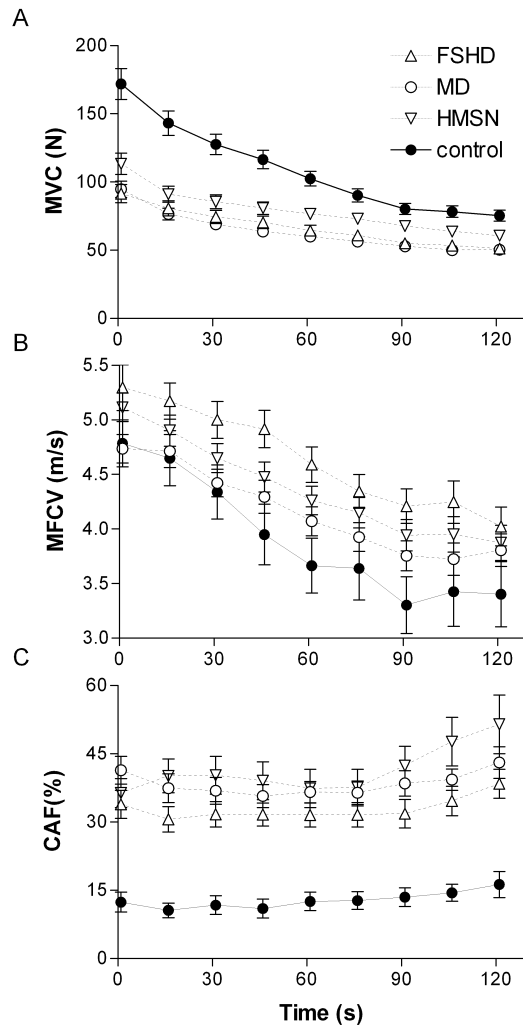


Fig. 8.2. Voluntary force (A), muscle fibre conduction velocity (B) and central activation failure (C) during a 2-min sustained MVC. At the start of the contraction, patients show lower voluntary force and higher central activation failure than controls. Voluntary force declines slower in patients than in controls.

Central activation failure and fatigue

At the start of the sustained MVC, patients showed higher CAF values than controls [$t = 8.9$; $p < 0.001$] (Fig. 8.2C, Fig. 8.3, Table 8.2). Values in the three patient groups were similar. CAF^0 correlated negatively with mean MRC in FSHD and HMSN [FSHD: $\rho = -0.27$, $p = 0.038$; HMSN: $\rho = -0.39$, $p = 0.004$]. It correlated positively with AFQ in HMSN [$r = 0.31$, $p = 0.022$], but not in the other patient groups nor in the control group. Taking an average CAF of the first 30 s MVC slightly reduced the variance of CAF

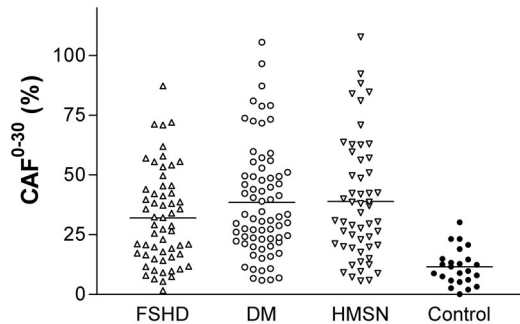


Fig. 8.3. Central activation failure in FSHD-, DM-, and HMSN-patients, and healthy controls at the start of sustained MVC. Each symbol represents a mean CAF of the first 30 s MVC within one individual. Horizontal lines show group averages. Patient groups clearly show higher mean values than the control group, although individual patients might have normal values. Theoretically, CAF values lie between 0 and 100%. In both DM and HMSN one artificially high value has been found, which must be ascribed to inaccuracy of the measurements.

values in controls, FSHD and MD. This CAF^{0-30} did correlate with AFQ scores in all three patient groups but not in controls, although p-values in FSHD were borderline [FSHD: $r = 0.26$, $p = 0.051$; MD: $r = 0.27$, $p = 0.022$; HMSN: $r = 0.32$, $p = 0.019$].

Only in the HMSN-group, the slope of CAF during the sustained contraction was significantly positive [slope = 0.10 (0.34)% s^{-1} , $t = 2.0$, $p = 0.046$]. However, ANOVA did not show a difference between this slope and the slopes of the other patient groups. Slopes of patients and controls did not differ significantly. Central fatigue, measured as the difference of CAF^{120} and CAF^0 , was significantly positive in HMSN [$t = 2.4$, $p = 0.019$], and not in the other groups. Though, again ANOVA did not reveal a difference between the three patient groups and central fatigue was not different between patients and controls. In none of the groups central fatigue correlated with mean MRC or AFQ.

Discussion

This study shows that more than 50% of the neuromuscular patients has severe experienced fatigue. In a sustained MVC protocol, total physiological fatigue and peripheral fatigue are smaller in neuromuscular patients, but central fatigue is similar in

patients and controls. Activation of the muscle by the central nervous system was shown to be less efficient in patients than in controls. The level of central activation failure correlated positively with the level of experienced fatigue. A remarkable similarity is present in all aspects of fatigue in the three groups of neuromuscular patients.

Experienced fatigue

Neuromuscular patients experience a high level of fatigue: patients' mean AFQ values were clearly higher than normal, both when compared to values measured in our control group and to reference values reported in literature². Correspondingly, CIS-fatigue scores of the neuromuscular patients were much higher than in the normal working population¹⁰. The correlation between AFQ and CIS-fatigue showed that the level of experienced fatigue at the current moment parallels the level of long-term fatigue.

Peripheral fatigue

Lower peripheral fatigability was present in patients compared with controls. This contrasts with the increased fatigability that was found during intermittent exercise in patients with amyotrophic lateral sclerosis¹⁵⁰, postpoliomyelitis syndrome¹⁴⁹ and multiple sclerosis¹⁰⁶. Schulte-Mattler and coworkers¹⁴³ described excessive peripheral fatigue during repetitive electrical stimulation in mitochondrial encephalomyopathies and a hodgepodge of other neuromuscular disorders, among which FSHD, MD and a polyneuropathy. In contrast to our work, both the intermittent exercise tasks and the non-tetanic contractions after electrical stimulation avoid vascular occlusion.

In our protocol, blood flow will have been occluded less in the majority of patients than in the controls. This results from the lower intramuscular pressure, due to the smaller MVC in patients¹⁸⁶. The ongoing blood flow keeps the intracellular state in patients better than in controls. If our protocol had avoided vascular occlusion in both patients and controls, results on peripheral fatigability possibly would have been more in line with the literature.

Peripheral fatigue was not related to the current level of experienced fatigue.

Central activation failure and fatigue

Central fatigue was minimal in all groups. In contrast to our former studies^{140,141}, even healthy controls did show no central fatigue. This may have to do with the higher age of the newly studied group. How central fatigue relates to age, seems to be task-dependent and possibly also depends on the methodology used for CAF assessment⁶. Our results do not show any relationship between central and experienced fatigue, which is not surprising regarding the very low central fatigue in all groups.

In contrast, CAF at the start of sustained MVC is greater in patients compared with controls, and does relate to the level of experienced fatigue.

Of importance for the discrepancy between physiological fatigue measures and the level of experienced fatigue is the difference in concepts. Physiological fatigue has been defined as an exercise-induced reduction in maximal voluntary muscle force⁴⁸. In contrast, experienced fatigue has been characterised as a difficulty in initiation of or sustaining voluntary activities²⁴. It is a state not necessarily induced by exercise. CAF at the start of sustained contraction is not influenced by exercise. This may explain why CAF correlates better with the level of experienced fatigue than the exercise-dependent physiological, peripheral and central fatigue.

As described above, CAF is higher in neuromuscular patients than in controls. This result seems to be in accordance with one of the findings of Di Lazzaro et al.³⁴. They showed an increased resting motor threshold in FSHD using transcranial magnetic stimulation (TMS), which might indicate lower resting membrane potentials of the cortical and/or spinal motoneurons²¹. In contrast, Liepert and co-workers⁹⁵ did not observe a different motor threshold in a group of 10 myopathic patients, including 6 FSHD patients. TMS in MD patients did not show a significant change in resting motor threshold, although it demonstrated a prolongation of central motor conduction time in patients, which was related to motor threshold value¹²¹.

Increased CAF also seems to contradict the lowered intracortical inhibition observed with TMS in FSHD and other myopathies^{34,95}. Enhanced excitability of α -motoneurons and increased amplitudes

of motor-evoked potentials, described in myopathies by Liepert et al.⁹⁵ do not seem to be consistent with our results. However, the translation of results of isolated short-pulse TMS experiments into the behaviour of the brain in a more natural situation remains difficult. Apparently, although some systems possibly promote enhanced activation, in neuromuscular patients the output from the total chain of motor activation is reduced.

It is unclear which factors cause the reduced central activation in FSHD, MD and HMSN. In general, reduced concentration, motivation and effort increase CAF values^{49,80,82,100}. We tried to diminish the contribution of these factors by actively encouraging the subjects and by providing real-time visual feedback of the performance¹⁵⁵. Pain, described as a symptom of these neuromuscular disorders^{20,22,127} or other feedback from muscles, joints and tendons may have reduced central activation^{49,58,133}.

Although muscle weakness is the most obvious symptom of FSHD, MD and HMSN, it cannot be excluded that other systems, e.g. the (central) nervous system, are affected. In FSHD, the peripheral afferent sensory pathways³⁸, and in MD functioning of the sensory cortex have been shown to be altered¹¹². Functional changes at the motor cortical level have been described in several neuromuscular disorders^{26,34,95,121}. These may be a consequence of deconditioning or the relatively large demands on the affected neuromuscular system in daily life. It is well known that recruitment of motor units in neuromuscular disorders is abnormal. In myopathies more motor units are recruited already at low force levels; in neuropathies on the other hand, force is mainly regulated by control of firing rate¹³⁸. In both circumstances the activation pattern of the central nervous system may not be suited to counteract the peripheral problems, resulting in suboptimal drive.

The level of experienced fatigue and CAF are correlated, although explained variance is limited. This suggests that experienced fatigue influences CAF. Though, we cannot exclude the reverse: CAF may (partly) control the experience of fatigue. In this light, it is interesting that patients with chronic fatigue syndrome, whose main complaint is the experience of severe fatigue, show greater CAF as well^{82,141}.

Finally, some pharmaceutical agents may influence CAF⁷⁶ by changing neuronal functioning. While about a third of our neuromuscular patients used any form of medication, we checked if this could explain the higher values of CAF in our group of patients. Sub group analyses, however, showed that CAF values of only medication-free patients were also increased.

Considering clinical practice, it is important to notice that MRC and MVC values can be strongly influenced by the amount of CAF. Reduced central activation further decreases the maximal voluntary force in neuromuscular patients who generally already have reduced muscle force because of changes in the muscle and/or nerve tissue. Therefore, these measures do not provide an objective evaluation of neuromuscular functioning. Especially in weaker patients conclusions about muscle functioning should be drawn with great care, because CAF and mean MRC turned out to be negatively correlated in two of the three patient groups. How it influences the daily life of patients is unclear. Compared to controls, patients will more often need a higher percentage of MVC to perform daily tasks. However, a task, like the one we used, is uncommon in daily life. If central activation is also diminished during short contraction is formally unknown, but seems to be likely considering the large CAF at the start of sustained contraction. Resistance training has been suggested as a way to reduce CAF, but conclusive evidence has not yet been provided¹⁵⁵. However, results of Lindeman et al.⁹⁶ indeed strongly suggest a reduction of CAF during a training program in HMSN patients.

In conclusion, this paper shows that although neuromuscular patients experience considerably more fatigue than healthy controls, neither central nor peripheral fatigue is increased. Already at the start of sustained MVC, neuromuscular patients show diminished central activation, which is correlated to the level of experienced fatigue. At present, we can only speculate about the cause of this central activation failure. For clinical practice, it is important to bear the consequences in mind.

Chapter 9

Contribution of central and peripheral factors to residual fatigue in Guillain-Barré syndrome

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Submitted

Abstract

The majority of neurologically 'well-recovered' Guillain-Barré syndrome (GBS) patients suffer from excessive fatigue. To dissect fatigue in these patients, we determined the relative contribution of peripheral and central factors during a fatiguing sustained maximal voluntary contraction (MVC) in these patients.

Ten fatigued but neurologically relatively 'well-recovered' GBS patients, and 12 age- and sex-matched healthy controls participated in this study. Experienced fatigue was evaluated using the Fatigue Severity Scale (FSS) and Abbreviated Fatigue Questionnaire (AFQ). Physiological fatigue was defined as the decline of voluntary force during a 2-min sustained MVC of the biceps brachii. The relative amounts of peripheral fatigue and central activation failure (CAF) were determined combining voluntary force and force responses to electrical stimulation. Additionally, surface EMG was used to determine muscle fiber conduction velocity (MFCV) during the contraction.

Experienced fatigue scores were significantly higher in patients than in controls. During the first minute of sustained MVC, peripheral fatigue developed slower in patients, and central fatigue occurred in patients but not in controls. The MFCV was higher in patients. The initial MVC, decrease of MVC, the initial force response and the initial CAF did not significantly differ between the groups.

Our results could well be the consequence of persistent axonal loss of motoneurons after GBS. This suggest involvement of peripheral changes in the pathogenesis of fatigue after GBS.

Introduction

Guillain-Barré syndrome (GBS), a monophasic immune-mediated disease of the peripheral nervous system, is characterized by acute symmetrical limb weakness and reduction or loss of myotatic reflexes as a consequence of nerve conduction (NC) failure^{18,60,170}. Various clinical and electrophysiological subtypes can be distinguished, ranging from a pure motor form to the classical demyelinating type of the disease^{18,60,170}. Despite relatively good neurological recovery, the majority of GBS patients remain severely fatigued¹⁰⁷. In order to elucidate possible 'peripheral' pathophysiological mechanisms of these fatigue complaints in GBS patients, conventional NC and conduction velocity distribution (CVD) studies have been performed⁵³. CVD values showed narrowing of the spectrum of different NC velocities, with loss of the extreme values, but a correlation between NC alterations and severe fatigue could not be found. Although fatigue is one of the most disabling residual symptoms and seriously affects quality of life, its pathophysiological mechanisms remain largely unknown.

Since different physical and psychological factors might contribute to fatigue in GBS^{54,107}, we hypothesize that residual fatigue in GBS has a peripheral neuromuscular origin, possibly combined with additional central components. The hypothesis of central nervous system involvement may be related to central white matter lesions, which can be found in some patients in the acute phase of GBS^{63,103,114,123,169}, or to the decreased concentrations of hypocretin in the liquor of some GBS patients, the pathophysiological hallmark of narcolepsia-cataplexia^{7,117}. Complaints of fatigue after GBS might also be of psychological origin, a consequence of a potentially life threatening disease like GBS.

To date it is possible to dissect the relative contributions of peripheral and central factors to physiological fatigue during a sustained contraction^{12,48,142,168}; force loss due to disturbances in the neuromuscular junction and muscle tissue are regarded as peripheral, and any disturbances in the nervous system as central. We used this technique to study the different aspects of fatigue

after GBS and discuss its possible underlying pathophysiological mechanisms.

Patients and Methods

Patient population

Eleven 'neurologically relatively well-recovered' GBS patients (defined as patients with GBS-disability score of 1 or 2)⁸⁴ participated in this observational study. All GBS patients initially suffered clinically from acute inflammatory demyelinating polyneuropathy (AIDP). In 7 patients an electromyogram (EMG) was available, supporting this initial clinical diagnosis of AIDP. The patients initially participated in a training intervention study on treatment of severe fatigue⁵⁴. Patients were eligible for this training study when they were severely fatigued (mean fatigue severity scale (FSS) score at least 5.0 out of 7.0)⁸⁸, and neurologically stable (no apparent change in GBS-disability score for at least 3 months)⁸⁴. All patients had been screened to exclude concomitant conditions (i.e. depression) or use of medication that might cause or influence fatigue. This training program improved self-reported fatigue scores, but self-experienced fatigue remained significantly increased in patients compared to controls⁵⁴. Twelve age- and sex-matched healthy controls were included. Controls were healthy volunteers or acquaintances of the examined patients. The local ethics committee of the Radboud University Nijmegen Medical Center approved the protocol and experiments were performed in accordance with the Declaration of Helsinki.

Assessment scales of experienced fatigue

Before the participants underwent the measurements, they were additionally evaluated using two assessment scales: the FSS and Abbreviated Fatigue Questionnaire (AFQ).

The FSS is a 9-item questionnaire with answers ranging from 1 ("strongly disagree") to 7 ("strongly agree") for each inquiry in relation to fatigue. The mean score of the 9 inquiries ranges from 1 ("no signs of fatigue") to 7 ("most disabling fatigue"). The FSS is a brief and simple self-assessed questionnaire, evaluating fatigue in the past week. The FSS was recently validated and examined in

terms of its reproducibility (internal consistency, reliability and validity, test-retest) in patients with immune-mediated polyneuropathies and translated into Dutch before its use^{88,107}. The FSS was completed before the start of the experiment.

The AFQ is a 4-item questionnaire. As in the FSS, each item is answered on a 7-point scale. Scores range from 4 to 28; a higher score indicates a higher level of self-perceived fatigue. The Dutch version of the AFQ was used. It was filled out just before the start and just after the end of the physiological measurement, referring to the level of experienced fatigue at the current moment^{1,2}.

Physiological factors of fatigue

Experimental set-up and protocol

The experimental setup has been published before^{140,141}. The protocol was based on the twitch interpolation technique⁴⁸. Subjects sat in a chair with their left arm fixed in a dynamometer in a horizontal position with the shoulder in abduction, the elbow in a right angle and the forearm supinated. Trunk and elbow were stabilized using custom made pads.

Initially, subjects made three short MVCs, each separated by a 1-min rest. Then, after a 10-min rest period, subjects were instructed to make a 2-min sustained MVC of their biceps brachii muscle. Before and directly after contraction, a stimulus event (described below) was applied to the relaxed muscle. During MVC, stimulus events were applied every 15 s, starting directly after the start of contraction.

Electrical stimulation

Electrical stimulation was applied over the motor points. To determine stimulus intensity and to get subjects used to stimulation, before the start of the protocol stimuli were applied repetitively to the relaxed muscle. Meanwhile, the current was increased until the force did not rise anymore. This intensity was used in all stimulus events.

A stimulus event consisted of five times a 5-pulse 100-Hz train (duration 40 ms). Pulse duration was 100 μ s. The average of the five force responses to the five short trains is referred to as 'the

force response' and is used for analysis. During voluntary contraction the inter-train interval was 325 ms, during rest the inter-train interval was 1000 ms. Pilot experiments showed that these inter-train intervals were appropriate to avoid fusion of the single force responses. Potentiation does not occur with this type of stimulus event. Therefore, it was not necessary to precede the initial stimulus event by a voluntary contraction.

Force analysis

The force of elbow flexion was measured at the wrist. Force was sampled at a rate of 2 kHz and low pass filtered (1 kHz). The maximal resolution of force measurement was 0.1 N bit⁻¹. The initial MVC was determined as the maximum value of the three short MVCs. During sustained MVC, voluntary force values reported are the averages of 1s of data directly before electrical stimulation. Force responses upon stimulation during sustained MVC were corrected for variations of voluntary force via linear interpolation between the moment of stimulation and 325 ms after.

Central activation failure (CAF^t) and peripheral fatigue (PF^t) at time t during sustained MVC were determined from the force data as described extensively elsewhere¹⁴². Thus, when F_{sx}^t is the superimposed force response to stimulation at time t , F^t is the actual MVC at time t (mean over 1 s of data) and β is the ratio of stimulated force over force capacity of the muscle, CAF^t is determined as

$$CAF^t = \frac{F_{sx}^t}{\beta \cdot F^t + F_{sx}^t}$$

The ratio β is determined using force values generated at the start and at the end of sustained MVC. The β used is the mean value calculated from these two moments. F_s^b represents the force response to stimulation during rest before sustained MVC, F_s^e after the end of sustained MVC. The suffixes 0 and T refer to the start and the end of sustained contraction, respectively. Thus:

$\beta = \text{mean}(\beta^0, \beta^T)$, in which

$$\beta^T = \frac{F_s^e - F_{sx}^T}{F^T} \text{ and } \beta^0 = \frac{F_s^b - F_{sx}^0}{F^0}$$

As described before¹⁴², peripheral fatigue at time t during sustained MVC is determined from the voluntary and stimulated force data as

$$PF^t = 1 - \frac{\beta \cdot F^t}{(1 - CAF^t) \cdot F_s^b}$$

The total amount of peripheral fatigue after the 2-min sustained MVC is also expressed as the relative change of force responses after electrical stimulation in rest after and before sustained MVC¹⁴⁰. Force analyses were performed in Matlab 6.5 (The MathWorks) and Microsoft Excel 2000.

SEMG analysis

Surface EMG (sEMG) was measured using a multi-electrode array of five gold-coated electrodes that were placed in line (electrode diameter 2 mm; inter electrode distance 3 mm) parallel to the fibre direction of the biceps brachii muscle, distal to the motor points. A reference electrode was placed at the elbow joint. During placement of the electrode array, both monopolar and bipolar EMG was monitored visually and values of impedances and cross correlations between the adjacent electrode positions were checked. If electrode placement was not satisfactory, the device was replaced.

Monopolar signals were amplified, bandpass filtered (3.2-800 Hz) and A/D-converted (16 bits with a resolution of 0.5 mV bit⁻¹ at a rate of 4 kHz/channel). A custom made time code generator synchronized force- and sEMG-data. SEMG analysis was done on 1 s of data just before stimulation. MFCV was determined from four out of five electrodes¹⁴⁰. The upper limit of MFCV was set at 8 m s⁻¹, based on physiological limits. SEMG analyses were performed in Matlab 6.5.

Statistical analyses

For each subject, linear regression analysis using the least squares method determined the slopes of CAF, PF, MFCV and MVC during the first minute, during the second minute and during the total 2-min sustained contraction. One-sample T-tests were used to test if slopes deviated from 0. Between-group differences were

analyzed with independent-samples T-tests. Pearson's correlations were performed to study the relationship between experienced fatigue and physiological fatigue variables. Significance level was set at $p \leq 0.05$ (two-tailed). Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS version 12.0.1).

Results

Baseline characteristics

Baseline characteristics are listed in Table 9.1. The measurement of 1 GBS patient failed due to technical problems, resulting in participation of 10 GBS patients and 12 age and sex matched healthy controls.

		GBS (n=10)	Controls (n=12)
Sex	Male	5	6
	Female	5	6
Years since diagnosis		6.9 (4.1-13.1)	--
Age		55.6 (48-67)	53.8 (31-69)
GBS-disability score at nadir		3.8 (2-5)	--
	F=2	1	--
	F=3	2	--
	F=4	5	--
	F=5	2	--
GBS-disability score at follow-up		1.1 (1-2)	--
	F= 1	9	
	F= 2	1	
FSS-score at follow-up			4.9 (2.9-6.9)
	≥ 5.0	4	--
	< 5.0	6	--
MRC-sumscore at follow-up		59.8 (58-60)	60 (60)
	60	9	12
	58	1	--

Table 9.1. Baseline characteristics. All values are given in means, and range included. GBS-disability score ranges: F = 0 (healthy, no symptoms or signs), F = 1 (minor symptoms or signs, capable of running), F = 2 (able to walk at least 10 meters across an open space without assistance, walking frame, or stick, but unable to run), F = 3 (able to walk 10 meters with walking frame, sticks or support), F = 4 (bed or chair bound, unable to walk), F = 5 (assisted ventilation required for at least part of the day or night); FSS score ranges from 1 (no signs of fatigue) to 7 (most disabling fatigue); MRC-sumscore ranges from 0 (paralysis) to 60 (normal strength).

Experienced fatigue

FSS

The mean self-reported fatigue scores as measured with the FSS were high (mean 4.9 (1.3), range 2.9 – 6.9, Table 9.1), similar to previous findings in GBS, and worse than scores previously obtained in healthy individuals (range 2.2 – 2.9, $p < 0.01$)^{54,107}. Four patients were still severely fatigued (mean FSS score at least 5.0). Controls only completed the AFQ.

AFQ

Answering the AFQ, patients reported a mean AFQ score of 11.7 (4.6; range 6 – 19), which was significantly higher than scores obtained in the healthy controls (7.8 (3.0), range 4 – 12; $p = 0.032$). AFQ values obtained directly after exercise showed a trend to have increased in patients (mean difference 3.10 (4.58); $p = 0.061$), but not in controls (mean difference 0.40 (5.05); $p = 0.808$).

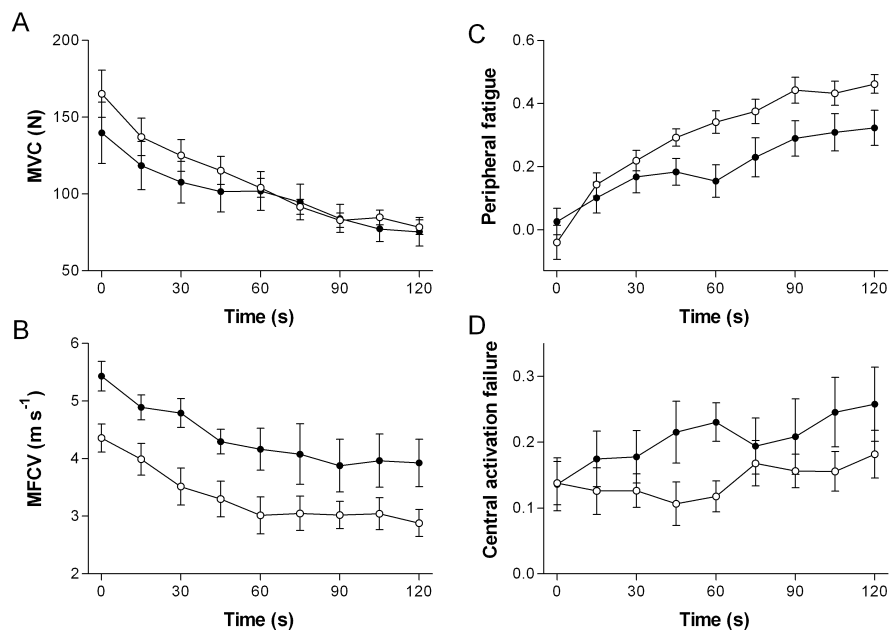


Figure 9.1 Maximal voluntary contraction (A), muscle fibre conduction velocity (B), peripheral fatigue (C), and central activation failure (D) for GBS patients and healthy controls during 2-min sustained MVC. Healthy subjects are represented by a '○', GBS patients by a '●'.

Physiological fatigue

The initial MVC, that is the short MVC obtained before the start of sustained contraction, was 177.6 (73.8) N in patients, which was not significantly lower than 204.0 (58.5) N in controls ($p = 0.361$). F^0 , that is the mean force produced over 1 s directly at the start of sustained MVC, neither differed significantly between patients and controls (patients: 139.9 (63.3) N; controls: 165.2 (53.0) N; $p = 0.318$; Fig. 9.1A). MVC decreased similarly ($p = 0.242$) during sustained MVC with 40.0 (20.0)% in patients and 49.2 (15.9)% in controls. The slopes of relative MVC decrease were similar in patients and controls (Table 9.2).

slope	First minute			Second minute		
	controls	GBS	p	controls	GBS	p
MVC ($\% s^{-1}$)	-.528(.262)	-.351(.301)	.156	-.238(.137)	-.344(.236)	.230
MFCV ($\cdot 10^{-1} ms^{-2}$)	-.216(.128)	-.178(.125)	.531	-.022(.102)	-.039(.099)	.711
PF ($\cdot 10^{-2} s^{-1}$)	.607(.291)	.226(.264)	.005	.199(.140)	.277(.286)	.412
CAF ($\cdot 10^{-2} s^{-1}$)	-.040(.165)	.153(.193)	.020	.077(.127)	.071(.190)	.925

Table 9.2. Slopes of maximal voluntary force (MVC), muscle fiber conduction velocity (MFCV), peripheral fatigue (PF) and central activation failure (CAF) during the first and second minute of sustained maximal voluntary contraction. During the first minute PF increases slower and CAF increases faster in patients than in controls.

Peripheral fatigue

The amplitude of the initial force response during rest did not significantly differ between patients and controls (patients: 11.3 (4.1) N; controls: 15.3 (6.8) N; $p = 0.124$). Directly after sustained MVC, this amplitude was declined by 33.5 (21.0)% in patients and by 45.9 (11.5)% in controls ($p = 0.120$). Fig. 9.1C shows the increase of peripheral fatigue in the course of sustained MVC. During the first minute of sustained MVC, peripheral fatigue increased slower in patients than in controls (Table 9.2). In contrast, during the second minute patient and control slopes were similar (Table 9.2). MFCV at the start of contraction was higher in patients than in controls (Fig. 9.1B; patients: 5.4 (0.7) $m s^{-1}$; controls: 4.4 (0.8) $m s^{-1}$; $p = 0.008$). Its relative decline during sustained MVC was similar in the groups, in the first as well as in the second minute of sustained MVC.

Central activation failure and fatigue

Fig. 9.1D shows that CAF did not differ between patients and controls directly at the start of sustained contraction (patients: 0.14 (0.13); controls: 0.14 (0.11); $p = 0.971$). In patients, CAF increased significantly during the first minute of sustained MVC ($p = 0.033$), whereas it did not deviate from zero in controls ($p = 0.425$). In the second minute, slopes of CAF were similar in patients and controls (Table 9.2). The total amount of central fatigue, defined as $CAF^{120} - CAF^0$, did not significantly differ between both groups (patients: 0.12 (0.18); controls: 0.04 (0.11); $p = 0.24$), although it seemed to deviate from zero in patients ($p = 0.065$), but not in controls ($p = 0.205$).

Correlations

We have tested correlations between FSS, AFQ or AFQ change scores and the physiological measures (CAF^0 , CAF^{0-30} , slopes of CAF, central fatigue, peripheral fatigue, slopes of peripheral fatigue, initial MVC, MVC at the start of sustained contraction, maximum possible force, and slopes of MFCV) for patients and controls separately. Significant correlations were only found between AFQ and the slope of CAF in the second minute in control subjects ($r = 0.729$, $p = 0.011$), and between AFQ and the slope of peripheral fatigue in the first minute in patients ($r = 0.666$, $p = 0.035$).

Discussion

The relative contributions of peripheral and central aspects of residual fatigue in neurologically 'well-recovered' GBS patients were determined during a 2-min sustained MVC. The main findings of this pilot study were slower development of peripheral fatigue during the first minute of this sustained contraction, a significantly faster occurrence of central fatigue, and a higher initial MFCV in GBS patients than in control subjects. The total amount of physiological fatigue and the course of MFCV did not significantly differ between both groups. These findings might be a consequence of persistent axonal loss of motor neurons after GBS. Several possible underlying mechanisms of fatigue are discussed.

Many patients recovered from GBS indicate their complaints of fatigue as endurance intolerance. This was supported by the experienced fatigue, determined with the AFQ. Fatigue values obtained directly before and after sustained MVC, showed a trend to increase by exercise in patients but not in controls. In contrast to results in patients with a current diagnosis of a neuromuscular disorder or chronic fatigue syndrome¹⁴¹, the initial CAF values in healthy subjects and GBS patients were similar. These previous studies suggest that central functioning might be related to the level of experienced fatigue. In GBS patients, no relation was found between the self-experienced fatigue and peripheral or central fatigue. In the GBS patients we examined, central fatigue occurred during the first minute of sustained MVC, whereas it could not be detected in healthy controls. In the latter part of the exercise, the levels of central fatigue in patients and controls were similar. Additional and different from GBS patients, patients with chronic fatigue syndrome suffer from severe fatigue all day long, and fatigue seems to be less specifically triggered by physical exercise¹⁷¹. This observation is supported by the CAF values; in patients with chronic fatigue syndrome these values are already increased at the start of a sustained MVC, while in GBS patients these values initially are normal, and only increase during the first minute of sustained MVC, supporting patients' opinion that fatigue after GBS seems more an endurance problem and exercise related.

The observation that peripheral fatigability in fatigued but neurologically 'well-recovered' GBS-patients was lower than in healthy controls is similar to previous observations in patients with (slowly) progressive neuromuscular disorders. Better muscular endurance in patients recovered from GBS compared to control subjects has also been reported in a recently published long-term follow-up study³⁶. Reduced peripheral fatigue might be a consequence of less occlusion of blood flow in the studied muscle; with smaller force production, and thus lower intramuscular pressure, occlusion of blood flow is reduced, and consequently, peripheral fatigue will also be reduced. GBS patients tended to have a lower MVC than healthy controls. This observation is in line with observations about long-term muscle strength values after GBS as described before^{36,54,179}. Many patients in these studies

seemed neurologically well recovered, reflected by normal functional scores and maximal MRC sumscores, but isokinetic muscle strength values were lower than in healthy controls. These decreased maximal muscle strength values may also be involved in the pathophysiology of fatigue. It was described previously that increased fatigability inevitably occurs in patients with muscle weakness, regardless of the different underlying peripheral or central or neurological disorders¹⁰⁶. We, however, did not detect a correlation between MVC and experienced fatigue. Finally, reduced peripheral fatigue might also be caused by a changed muscle fiber type composition after recovery from GBS. Supported by the significantly higher MFCV in patients, we hypothesize that recovery after GBS is accompanied by reinnervation of muscle fibers. Part of the fibers, however, may be lost. To restore muscle strength, the reinnervated muscle fibers become hypertrophic, which increases MFCV. It can be hypothesized that the occurrence of central fatigue is related to the decreased number of remaining motor units¹⁰⁴. Changed muscle organization may require different demands on the central nervous system. The normal interplay between number of recruited MUs in relation to the firing frequency is disturbed. It could well be that the smaller number of motor axons in GBS gives rise to the relatively fast increase in CAF during the first minute since the dropout of only a few MUs could already give rise to a relatively large central activation failure.

Some methodological issues of the current study should be addressed. The experimental setup of the 2-min sustained contraction, in which patients are actively encouraged, was used to discriminate between peripheral and central aspects of fatigue. This experimental situation is different from normal daily life, in which a sustained MVC is used much less than for example repetitive or cyclic muscle contractions. A test that had avoided blood occlusion in all subjects, like cyclic muscle contractions, additionally could have led to different results regarding peripheral fatigue. The recent finding of reinnervation in many neurologically well-recovered GBS patients^{27,36}, in combination with the to be expected changes in muscle anatomy, might suggest that other electrophysiological techniques like estimation of motor-unit numbers (MUNE) can be of additional value. Only a few studies are

performed using MUNE techniques in GBS^{90,104}, but its relationship with fatigue was never studied. Additionally, many FSS items are based on physical consequences of fatigue. Because many patients indicate their fatigue as a result of impaired endurance intolerance, this might indirectly lead to an overestimation of these complaints of fatigue. However, our patients were neurologically seen 'well-recovered' and it is known from other studies that the FSS is an adequate tool to evaluate fatigue^{35,54,107,166}. Finally, we only found a few significant correlations between physiological measures of fatigue and experienced fatigue severity. This might be due to the relatively small number of subjects in this study.

To conclude, this pilot study was feasible for neurologically 'well-recovered' GBS patients and revealed valuable data concerning possible underlying pathophysiological mechanisms of their self-experienced fatigue. Physiological parameters showed faster occurrence of central fatigue and slower development of peripheral fatigue in the first minute of sustained MVC in GBS patients. These results, together with the increased MFCVs, suggest that peripheral changes after GBS may contribute to the experienced fatigue. A larger, prospective and controlled study, including electrophysiological measurements like CAF and MUNE and aiming to elucidate the mechanisms of fatigue after GBS, is warranted in fatigued compared to non-fatigued patients.

Section 4

Epilogue

Chapter 10

Summary and general discussion

The aim of this thesis was to study physiological aspects of fatigue in neuromuscular disorders and chronic fatigue syndrome (CFS). In the general introduction (chapter 1) three main research questions were addressed, that correspond to the themes of the first three sections of this thesis. This combined summary and discussion first will debate these questions. Then, it will shortly give some general considerations and finally present a discussion with regard to the main finding of this study: diminished central activation in fatigued patients.

Section 1: Frequency of experienced fatigue in neuromuscular disorders

The first section of this thesis describes the, both clinical and scientific, relevance of a study into fatigue in neuromuscular disorders. Literature reviewed in chapter 2 has already shown the presence of chronic severe experienced fatigue in several diseases, among which CFS. Though, until recently fatigue was seldom recognized as an important symptom of neuromuscular disorders. Chapter 3 shows that severe fatigue is experienced by more than 60% in a group of patients with three relatively common chronic neuromuscular disorders. Because in these patients severe experienced fatigue is associated with problems in physical functioning, social functioning, mental health, bodily pain, and general health perception, it is a clinically and socially relevant problem.

Behavioural and psychological aspects may play a role in the fatigue experience. However, especially in patients with neuromuscular disorders in whom the motor of the body itself (the muscles and/or nervous system) is affected, it is interesting to study the contribution of physiological factors to experienced fatigue. The successive chapters of this thesis therefore focus on physiological fatigue, which is defined as the loss of force producing capacity during exercise. If this loss has its origin at the neuromuscular junction or in the muscle tissue, it is called peripheral fatigue. If it occurs because of changes in the nervous system during exercise, it is named central fatigue. In the case voluntary central activation is sub-optimal, central activation failure

(CAF) is present; the *increase* of CAF during exercise is called central fatigue.

Section 2: Methods to measure physiological fatigue

The second section of this thesis describes some methods to assess both peripheral and central aspects of physiological fatigue. The chapters 4 and 5 introduce an experimental protocol to determine these aspects simultaneously. Subjects make a 2-min sustained maximal voluntary contraction (MVC) of the biceps brachii muscle, during which electrical endplate stimulation is applied every 15 s. Separating peripheral and central aspects of fatigue is complex because the force superimposed by electrical stimulation is not only influenced by the level of voluntary central drive, but also by the amount of peripheral fatigue that has already developed. In chapter 4 we approach this problem by assuming that peripheral fatigue increases linearly during sustained MVC.

Chapter 5 shows that this assumption of linearity cannot be rejected in the particular case of a 2-min sustained MVC. However, it does not agree with physiological knowledge. Moreover, muscle fibre conduction velocities, presented as indicators of peripheral functioning, show a non-linear course of peripheral changes during sustained MVC. Chapter 5 therefore presents a model based approach to quantify CAF in the course of a sustained contraction that does not need the assumption of linearity. This method is based on the idea that a constant relative fraction of maximal possible force is activated by electrical stimulation, and that this fraction is representative for the total muscle. This assumption is virtually always made implicitly in central fatigue studies. With the model, CAF can be calculated during sustained MVC merely using voluntary and stimulated force data. The course of peripheral fatigue becomes available as well.

Both methods show that in healthy young subjects central activation at the start of a sustained MVC is sub-optimal. Mainly during the second minute of sustained contraction, central drive worsens, that is central fatigue occurs. The contribution of peripheral fatigue to the total force decline, however, by far exceeds the contribution of central fatigue.

The final chapter of the methodological section (chapter 6) presents a complementary approach to study central aspects of fatigue. In this case, subjects are instructed to make repetitive voluntary handgrip contractions at a level of 70% MVC. The readiness potential, a negative movement-related cortical EEG potential that appears over the human scalp about one second or more before a self-paced motor act, is recorded. The changing area of this potential, together with a constant force production and the virtual absence of peripheral fatigue, shows central adaptations to avoid or counteract central fatigue. In comparison with the earlier methods, this protocol provides a measure to study central aspects of fatigue at a level more upstream in the nervous system, namely at the motor cortex. Chapter 6 shows that in healthy subjects changes occur at the cortical level during repetitive contractions in the almost absence of peripheral fatigue.

Which of the above techniques is best for the study of physiological fatigue depends on the specific hypothesis to be tested.

Section 3: Physiological fatigue in patients

In the third section of this thesis the 2-min sustained MVC protocol is applied to several groups of severely fatigued patients. First, chapter 7 shows results on patients with the chronic fatigue syndrome (CFS), severely fatigued patients without a somatically explained disease. The results show that central activation is strongly diminished in this group: all individual CFS patients could have been identified on the basis of only their CAF value at the start of sustained contraction. Probably as a consequence of the smaller demands on the muscle because of diminished central activation, these patients showed less peripheral fatigue than healthy controls. Although it has not been tested formally, the results suggest a relation between the levels of experienced fatigue and central activation failure.

As has been described in section 1, we found that many patients with a chronic neuromuscular disorder experience severe fatigue. Chapter 8 describes that in the overall group of these patients, central activation is reduced with about the same amount as in CFS patients. However, the inter-individual distribution of the levels of

central activation is much larger and a clear overlap exists between patients and controls. A significant correlation exists between the value of central activation failure at the start of sustained MVC and the level of momentary experienced fatigue. Again, the amount of peripheral fatigue is reduced, probably because of the lower MVC of patients.

Finally, chapter 9 presents physiological measures of fatigue in patients neurologically well-recovered from Guillain-Barré syndrome (GBS). Whereas central activation failure at the start of sustained contraction was increased in patients with CFS and chronic neuromuscular disorders, it is normal in recovered GBS patients. However, it increases faster than in healthy controls, that is, central fatigue develops more quickly. At the same time, peripheral fatigue develops slower. In the above groups smaller peripheral fatigue is accompanied by lower MVC in patients, but patients recovered from GBS do not show a significantly lower MVC than control subjects. In addition, in contrast to the other groups, recovered GBS patients show increased muscle fibre conduction velocities. The small group of patients prohibited reliable determination of correlations. However, again the results suggest that the pattern of central activation and the experience of fatigue are related.

General considerations

The main finding of this thesis is that central activation is diminished or decreases faster in patients who experience severe fatigue. Suboptimal activation means that the motor unit firing rate or motor unit recruitment is suboptimal. Figure 10.1 illustrates the concepts of fatigue and CAF in controls and patients during sustained MVC. In healthy controls (left upper panel), CAF is about 15% at the start of contraction, which means that the maximal voluntary contraction is about 15% lower than maximal muscle capacity. During sustained MVC the amount of CAF increases, implying that central fatigue occurs. How much central fatigue develops, seems to be age dependent. In young subjects it is about 15%, in older ones central fatigue is almost negligible. In patients with CFS (left lower panel), muscle capacity is the same as in control subjects, but the force production during MVC is reduced

because of CAF values of more than 30%. In contrast, in patients with a chronic neuromuscular disorder (right upper panel) the maximum muscle capacity is reduced as a direct consequence of peripheral changes due to the disease. In addition, large CAF values similar to those in CFS patients further decrease force production during MVC. In both patients with CFS and the studied chronic neuromuscular disorders hardly any central fatigue occurs. Finally, in patients recovered from GBS (right lower panel), CAF at the start of sustained MVC is normal (about 15%), but it increases faster than in the control groups, which means that more central fatigue develops in this group of patients.

The studies presented in this thesis indicate that central activation failure and central fatigue are related to the experience

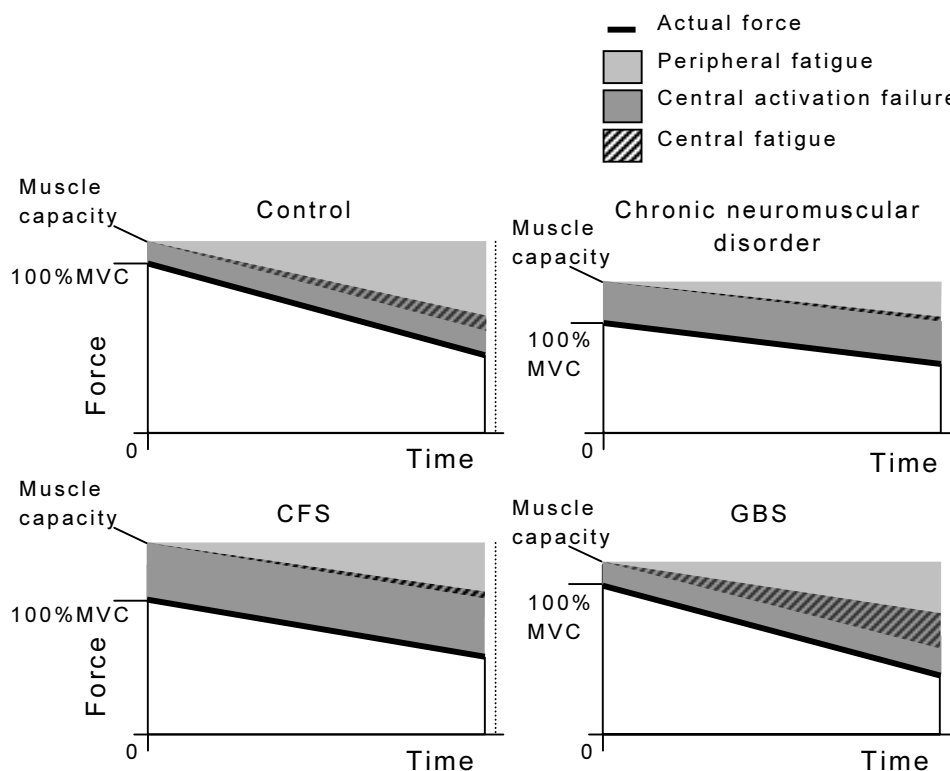


Figure 10.1. Peripheral fatigue, central fatigue and central activation failure in healthy subjects and patients with chronic neuromuscular disorders or chronic fatigue syndrome and patients recovered from Guillain-Barré syndrome. Vertical bars at the right of every figure show a constant force level in the panels.

of fatigue. In the case of chronic neuromuscular disorders, central activation failure explains 6 to 10% of the variance in the level of experienced fatigue. This weak relationship can only be detected if large numbers of patients are studied and therefore – if present – is not clear in our CFS and GBS studies.

In all patient groups, the amount of peripheral fatigue or rate of peripheral fatigue development is lower than in healthy controls. To a large extent, this is probably caused by the lower absolute force level at which patients perform the task. Because of the lower intramuscular pressure in the majority of patients, blood flow is hindered less, keeping the intracellular state in patients better than in controls. Thus, it is important to notice that this experiment does not provide conclusive evidence about possible differences in peripheral fatigability between patients and controls. Only in the particular case of GBS patients, the increased absolute muscle fibre conduction velocity gives a clue for changes at the peripheral level that may influence peripheral fatigability. To avoid a different influence of blood flow in patients and controls, in future studies blood flow occlusion may either be prevented or artificially achieved. It may be prevented by investigating repetitive contractions or voluntary or electrically stimulated contractions at a submaximal force level. Occlusion can be achieved by the use of a cuff.

Below I will discuss possible causes of diminished central activation and how event related potential studies can be used to determine which of these causes are probable. To conclude, some remarks about treatment will be made.

Causes of reduced central activation

Reduced voluntary central activation or the faster occurrence of central fatigue is not unique for the disorders we have studied. Diminished central activation has been described earlier in ankle dorsiflexors of ALS patients⁸¹, in hemiparetic quadriceps muscle after stroke¹¹⁶, in elbow flexors of post-polio patients⁵, in ankle dorsiflexors and elbow flexors of patients with chronic fatigue syndrome^{82,141}, and in quadriceps muscle of fibromyalgia patients^{118,119}.

Potential causes of reduced central activation can be various and will vary between disorders. Impaired concentration, reduced motivation and reduced effort will inevitably lead to suboptimal performance^{4,49,80,82,100}. During our studies, we tried to keep motivation as strong as possible by giving active verbal encouragement and providing real-time visual feedback¹⁵⁵. Especially in patient groups fear of physical movement and activity may be factors involved.

Pain is known to possibly influence the level of central activation^{58,133} and has been described as a symptom of all disorders we studied^{20,22,43,127}. Unpublished results of our group show that pain indeed correlates significantly with CAF in FSHD and shows a trend to correlate with CAF in HMSN, but not in MD. Central activation might also be altered by disturbed perception of task performance. In this respect, it may be relevant that peripheral afferent sensory pathways can be subclinically affected in FSHD³⁸ and considerably altered in HMSN. In MD functioning of the sensory cortex is modified¹¹², possibly influencing perception. CFS patients report relatively high perceived effort during exercise^{44,55,56,101,135}. Its cause is unknown, but the unbalanced experience may reduce central activation.

In addition to possibly changed perception, alterations at the (pre-) motorcortical level may decline central activation in patients. Neuromuscular disorders are most obviously characterized by muscle weakness, but we cannot exclude that other structures, among which the central nervous system, are affected. Especially in MD^{26,156}, but also in FSHD⁴⁵, cognitive brain functions can be altered, and in MD^{26,156} and CFS^{28,92} structural changes in the brain tissue have been revealed. Functional changes at the motorcortical level were described in chronic neuromuscular disorders^{26,34,95,121}. Additionally, especially in fatigued patients one might expect deconditioning to have induced neuronal adaptations. On the other hand, the relatively large demands on affected neuromuscular systems in daily life possibly have also influenced the central systems. In this respect, it is important to see that recruitment of motor units in neuromuscular disorders is abnormal: in FSHD and MD more motor units are recruited already at low force levels, in HMSN force is mainly regulated by the control of

firing rate¹³⁸. In the case of clinical recovery after GBS, the nervous system seems to deal with changes comparable to those in HMSN: the number of motor units has probably declined. In addition, our findings indicate that muscle fiber size has increased. In such circumstances, the activation pattern generated by the central nervous system may not be adapted to the peripheral changes. The different activation patterns in HMSN and GBS patients might be explained by the fact that HMSN is a chronic and GBS an acquired disease.

Further research into the cause of reduced central activation

To discover the cause of reduced central activation, further studies should be done. In this respect, for example functional magnetic resonance imaging or transcranial magnetic stimulation may be useful techniques. Chapter 6 presented the use of the readiness potential to study central adaptations that avoid the occurrence of physiological fatigue during repetitive contractions. Applying this technique on groups of fatigued patients may help to find the cause of reduced central activation or the faster occurrence of central fatigue. I will shortly describe the results of a study in which fatigued CFS patients were tested with the protocol presented in

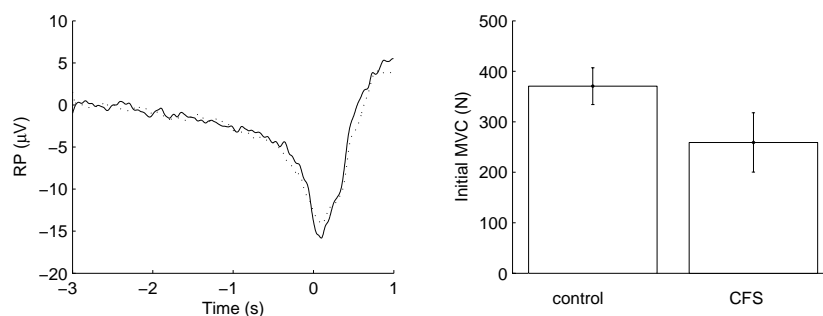


Figure 10.2. Normal readiness potential in patients with the chronic fatigue syndrome. The left panel shows the readiness potential during the first six minutes of repetitive force grip contractions at 70% MVC. The solid line represents control data, the dotted line patient data. The right panel shows that the MVC before exercise is higher in controls than in patients. This means that patients perform the 70% MVC task at an absolutely lower force level.

chapter 6. This study is as yet unpublished and has not been described in this thesis, but provides deeper insight into the possible cause of reduced central activation in CFS patients. Besides, it illustrates how event related potential studies may help elucidating the cause of reduced central activation.

Fifteen female CFS patients and fourteen female healthy subjects made repetitive handgrip contractions at 70% MVC. The initial MVC of the patients was about 30% lower than that of the control subjects (Fig. 10.2), which suggests the presence of increased central activation failure, as we found before. Patients thus performed the task at an absolutely lower force level than the control subjects. From literature^{8,41} we know that in healthy subjects the size of the readiness potential is related to the amount of voluntary force. Though, unexpectedly, the readiness potential at the start of the 30-min exercise was similar in the two groups (Fig. 10.2). This means that the output in terms of muscle force is smaller in CFS patients than one would expect on the basis of the readiness potential size. This phenomenon resembles the situation in healthy subjects after a longer period of repetitive contractions: the force output is relatively low compared to the size of the readiness potential. Anatomy shows that the motor cortex is monosynaptically connected to the motor neuron. This favours the idea that motor cortex function is less efficient in CFS and seems to invalidate reduced motivation as the main problem in CFS. However, chains between the motor cortex and the end of the motor nerve, and the influence of additional nuclei on the α -motoneuron should be studied extensively to support this hypothesis.

As far as I know, the readiness potential has not been studied in fatigued patients with a neuromuscular disorder, but in future this type of studies may indicate which of the above mentioned possible causes of diminished central activation are plausible.

Considerations about improving central activation

Diminished central activation will further reduce the maximal voluntary force output in patients whose force is already diminished because of the direct influence of a neuromuscular

disorder. Therefore, it may be desirable to improve central activation.

If large CAF values are caused or perpetuated by cognitive factors, psychological therapy might be helpful. In CFS patients, cognitive behaviour therapy directed at the maintaining factors of fatigue turned out to be effective to decrease experienced fatigue¹³¹. Physical training has been suggested as a way to reduce CAF¹⁵⁵, but Herbert et al.⁶⁷ did not notice a positive effect of physical training on central activation in healthy subjects. Of course, the size of CAF in fatigued patients provides a much larger scope for improvement. Lindeman et al.⁹⁶ report a 21% increase of MVC in combination with a 25% increase of surface EMG amplitude during a training program in HMSN patients. This EMG increase suggests an improvement of central activation. Although a balanced intensity of the training program should be chosen to prevent possible further muscle damage, physical training therefore might provide a method to improve central activation.

At first sight, reduced central activation seems to be a negative effect for patients. However, in chronic neuromuscular disorders it may also be seen as a positive adaptation, which protects the affected muscles or nerves against further damage. Therefore, we should not try to diminish it without concern. How it influences the daily life of patients is unclear. Compared to controls, patients will more often need a higher percentage of MVC to perform daily tasks. However, a task like the 2-min sustained MVC, is uncommon in daily life. Sustained maximal voluntary force is not often required. If central activation is also diminished during short contraction is formally unknown, but it is not unlikely considering the large CAF at the start of sustained contraction.

Future studies hopefully will reveal why central activation is increased or increases faster in fatigued patients and will prove if therapy has a positive effect, both on CAF and on the level of experienced fatigue.

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Samenvatting

Dit proefschrift behandelt fysiologische aspecten van vermoeidheid bij mensen met een neuromusculaire aandoening oftewel een ziekte van de spieren en/of zenuwen. De drie hoofdvragen zijn: 1) Komt vermoeidheid veel voor bij neuromusculaire aandoeningen? 2) Hoe meten we fysiologische vermoeidheid? 3) Hangt ervaren vermoeidheid bij patiënten samen met fysiologische vermoeidheid? In de drie voorgaande delen (sections) van dit proefschrift worden deze vragen een voor een beantwoord. In dit hoofdstuk vat ik de belangrijkste bevindingen samen.

Vermoeidheid bij neuromusculaire aandoeningen

Het eerste deel van dit proefschrift beschrijft de, zowel klinische als wetenschappelijke, relevantie van een onderzoek naar vermoeidheid bij mensen met een neuromusculaire aandoening. Hoofdstuk 2 geeft een samenvatting van de literatuur die ernstige ervaren vermoeidheid bij uiteenlopende aandoeningen bespreekt. Bij neuromusculaire aandoeningen wordt vermoeidheid zelden als symptoom herkend. Hoofdstuk 3 laat echter zien dat meer dan 60% van de patiënten met een neuromusculaire aandoening chronisch ernstig vermoeid is. De vermoeidheid gaat gepaard met verschillende functionele beperkingen in het dagelijks leven en is daarom een klinisch en sociaal relevant probleem.

Uit eerder onderzoek is bekend dat gedragsmatige en psychologische factoren een rol kunnen spelen bij het ervaren van vermoeidheid. Juist bij patiënten met een aandoening aan het zenuw- en/of spierstelsel is echter te verwachten dat ook fysiologische aspecten van belang zijn. De volgende hoofdstukken van het proefschrift richten zich dan ook op fysiologische vermoeidheid. Dit is gedefinieerd als een vermindering van de maximale vrijwillige kracht als gevolg van inspanning. Zowel perifere (spier-) als centrale (zenuwstelsel-) aspecten kunnen aan fysiologische vermoeidheid bijdragen.

Methodes om fysiologische vermoeidheid te meten

Het tweede deel van dit proefschrift behandelt een aantal methodes om zowel perifere als centrale aspecten van vermoeidheid te meten. De hoofdstukken 4 en 5 beschrijven een techniek om beide aspecten tegelijkertijd te kwantificeren. Voor deze meting spant de proefpersoon zijn bovenarmspier (m. biceps brachii) twee minuten lang zo hard mogelijk aan. Tijdens de vrijwillige aanspanning wordt de eindplaat van de zenuw elke 15 seconden elektrisch gestimuleerd. Het is lastig om de perifere en centrale aspecten van spierversmoeidheid te onderscheiden, doordat de extra kracht die door de elektrische stimulatie wordt opgewekt zowel door het niveau van vrijwillige centrale activatie als door de al opgetreden perifere vermoeidheid wordt beïnvloed. In hoofdstuk 4 lossen we dit probleem op door aan te nemen dat perifere vermoeidheid in de tijd lineair toeneemt. Hoofdstuk 5 laat zien dat dit in het specifieke geval van een twee minuten durende volgehouden maximale aanspanning acceptabel is. De aanname komt echter niet overeen met fysiologische voorkennis en bovendien laat het verloop van de spiervezelgeleidingssnelheid (een maat voor het perifere functioneren) een niet-lineair verloop in de tijd zien. In hoofdstuk 5 presenteren we daarom een modelmatige aanpak om het gebrek aan centrale activatie tijdens een langdurige aanspanning te kwantificeren zonder deze aanname nodig te hebben. Deze nieuwe methode is gebaseerd op het idee dat elektrische stimulatie een constant gedeelte van de spier stimuleert en dat dit gedeelte representatief is voor de hele spier. Vrijwel alle vermoeidheidsonderzoekers die vrijwillige aansturing via een vergelijkbare techniek meten, doen deze aanname, maar de aanname is niet eerder expliciet geformuleerd en uitgewerkt. Met het opgestelde model kunnen we het gebrek aan centrale activatie in de loop van een langdurige oefening bepalen aan de hand van gegevens over alleen vrijwillige en gestimuleerde kracht. Het model heeft bovendien het voordeel dat deze ook perifere vermoeidheid tijdens de oefening kan bepalen.

Beide methodes laten zien dat bij gezonde proefpersonen tussen de 18 en 40 jaar centrale activatie aan het begin van een volgehouden maximale vrijwillige aanspanning niet optimaal is. In de loop van de tijd verslechtert de aansturing verder, wat betekent

dat centrale vermoeidheid optreedt. De bijdrage van perifere vermoeidheid aan het totale krachtverlies overstijgt echter veruit de invloed van centrale componenten.

Hoofdstuk 6 presenteert een totaal andere aanpak om centrale aspecten van vermoeidheid te bestuderen. In dit geval krijgen de proefpersonen de opdracht om gedurende een half uur om de zeven seconden kort te knijpen tot 70% van de eigen maximale vrijwillige kracht. Het gaat hierbij om de zogenaamde readiness potential, een negatieve 'event related potential' (ERP) die ruim een seconde voor het begin van een zelfgeïnitieerde aanspanning in het EEG verschijnt. De grootte van deze potentiaal biedt een maat om tijdens een oefening veranderingen hogerop in het centrale zenuwstelsel te bestuderen, namelijk in de motorcortex. Uniek aan de methode is dat deze geen kunstmatige input behoeft. Bovendien heeft ze het voordeel dat aan vermoeidheid gerelateerde veranderingen bestudeerd worden tijdens meer natuurlijke repetitieve en submaximale aanspanning. Hoofdstuk 6 laat zien dat je met deze methode bij gezonde mensen aan kunt tonen dat er centraal veranderingen optreden die vermoeidheid voorkomen.

Het hangt van de precieze onderzoeksvraag af welke van bovenstaande technieken voor een bepaalde studie het meest geschikt is.

Fysiologische vermoeidheid bij patiënten

In het derde deel van dit proefschrift wordt het hierboven beschreven protocol van de twee minuten volgehouden maximale aanspanning toegepast op verschillende groepen ernstig vermoeide patiënten. Hoofdstuk 7 behandelt de resultaten bij patiënten met het chronisch-vermoeidheidssyndroom, mensen met ernstige vermoeidheidsklachten die geen aantoonbare lichamelijke aandoening hebben. De centrale aansturing van de spieren is bij deze groep mensen sterk verminderd. Dit verschil bestaat zelfs op individueel niveau: de centrale activatie is bij iedere onderzochte patiënt kleiner dan bij elke persoon uit de controlegroep. Tijdens de meting treedt bij de patiënten minder perifere vermoeidheid op dan bij de controlepersonen. Dit komt waarschijnlijk doordat de spiercapaciteit door de verslechterde aansturing tijdens de meting

in mindere mate aangesproken wordt. De resultaten van dit onderzoek suggereren dat er een relatie bestaat tussen de ervaren vermoeidheid en het gebrek aan centrale aansturing, maar dit is niet formeel getoetst.

Uit hoofdstuk 8 blijkt dat patiënten met een chronische neuromusculaire aandoening soortgelijke resultaten laten zien. Gemiddeld genomen is de centrale aansturing bij de groep patiënten ongeveer even sterk verminderd als bij de mensen met het chronisch-vermoeidheidssyndroom. De spreiding van de mate van vrijwillige activatie binnen de groep mensen met een neuromusculaire aandoening is echter veel groter en er bestaat een duidelijke overlap met de waarden van gezonde controlepersonen. Ook bij de groep patiënten met een chronische neuromusculaire aandoening is de hoeveelheid perifere vermoeidheid gereduceerd, waarschijnlijk als gevolg van de lagere maximale vrijwillige kracht. Het gebrek aan centrale aansturing bij de start van de maximale vrijwillige aanspanning correleert significant met het niveau van de ervaren vermoeidheid. De mate van perifere vermoeidheid hangt niet met de ervaren vermoeidheid samen.

Hoofdstuk 9 beschrijft tenslotte de aspecten van fysiologische vermoeidheid bij patiënten die zijn hersteld van het Guillain-Barrésyndroom, een acute ontsteking van de zenuwen. Na deze aandoening komen vermoeidheidsklachten veel voor. Hoewel bij de andere groepen vermoeide patiënten de centrale aansturing aan het begin van de oefening verminderd was, is dit niet het geval bij deze patiënten. Het gebrek aan centrale activatie neemt echter wel sneller toe dan bij controlepersonen, wat betekent dat centrale vermoeidheid versneld optreedt. Tegelijkertijd ontstaat perifere vermoeidheid juist trager. Doordat we slechts tien van Guillain-Barré herstelde patiënten hebben gemeten, is het niet mogelijk om betrouwbare correlaties te berekenen. De resultaten suggereren wel dat de ervaren vermoeidheid wederom samenhangt met het patroon van centrale activatie.

Conclusie

Uit het gepresenteerde onderzoek blijkt dat vermoeidheid een relevant probleem is bij patiënten met, of hersteld van, een

neuromusculaire aandoening. De mate en aard van de ervaren vermoeidheid lijken samen te hangen met het patroon van aansturing van de spieren door het zenuwstelsel. Waardoor de aansturing in patiënten verminderd is of sneller verslechtert, is nog onduidelijk. Mogelijk kunnen ERP-studies een bijdrage leveren aan het vaststellen van de oorzaak. Vervolgonderzoek is nodig om methodes te ontwikkelen waarmee de centrale aansturing bij patiënten verbeterd en zo de ervaren vermoeidheid mogelijk beperkt kan worden.

List of publications

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Dankwoord

Promoveren wordt vaak beschouwd als een moeizaam en zwaar traject, dat lange tijd ten koste gaat van het privéleven. Met goede begeleiding is het echter ook mogelijk binnen een parttimeaanstelling en zonder grote persoonlijke opofferingen. Dit vereist wel een werkomgeving waarin de verwachte prestaties reëel zijn en waarin de promovendus van verschillende kanten hulp krijgt. Een proefschrift maak je namelijk niet alleen: veel mensen hebben op verschillende manieren bijgedragen aan de voltooiing van dit proefschrift. Met dit hoofdstuk wil ik de hieronder genoemde personen hartelijk bedanken voor de rol die ze de afgelopen jaren voor mijn promotie hebben gespeeld.

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De meeste gepubliceerde ERP-metingen zijn gedaan door Maarten. Ook toen zijn stage officieel al afgerond was, heeft hij mij hiermee nog veel werk uit handen genomen.

Veel andere medewerkers van de afdeling klinische neurofysiologie zijn bij het project betrokken geweest, al is hun bijdrage vaak

minder concreet. Inhoudelijk heeft Dick een belangrijk aandeel geleverd door het stimuleren van methodische ontwikkelingen. Het meest waardeer ik echter zijn toegankelijkheid en sociale betrokkenheid bij de onderzoekersgroep. Joleen heeft ervoor gezorgd dat ik op de afdeling terecht ben gekomen en stond hiermee aan de basis van mijn onderzoeksproject. Bernd, Bert, Caroline, Edwin, Gea, Gijs, Jan, Mark, Mireille, Norbert, Robert en Sigrid wil ik bedanken voor zowel het inhoudelijk overleg als voor de gezelligheid en goede sfeer. Met name de dagelijkse wandeling in het park leverde extra energie voor het werk.

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Onverwachts is aan het einde van mijn onderzoekstijd een samenwerkingsproject ontstaan met de Erasmusuniversiteit te Rotterdam. Marcel, ik vond het verrassend dat we digitaal zo'n efficiënt en tegelijkertijd prettig contact konden hebben. Als alle publicaties zo vlot zouden verlopen, hadden we beiden al twee boekjes vol.

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Curriculum vitae

Maartje Schillings was born on August 25, 1976 in Nijmegen, the Netherlands. After finishing 'gymnasium' at the Stedelijk Gymnasium Nijmegen in 1994, she started her Biology studies at the Radboud University Nijmegen. She did a first internship at the Department of Medical Physics and Biophysics, where she studied perception of the subjective vertical during roll tilt. Her second internship was at the Department of Animal Physiology. This project focused on Ca^{2+} oscillations in melanotrope cells of the amphibian *Xenopus laevis*. In 1999 she received her masters degree and took on a job at the Department of Clinical Neurophysiology of the Radboud University Nijmegen Medical Centre. She was involved in the determination of electrical motor unit size from multi-channel surface EMG measurements in postpolio patients. In 2001 she started her PhD project on fatigue in neuromuscular disorders at the same department, of which this thesis is the result. Currently, Maartje is employed as a medical advisor by Excerpta Medica, an Elsevier business, in Amsterdam.

